REMARKS

Claims 1-94 were present in the application as filed. In response to a restriction requirement, Applicants elected Group II, claims 1-18, 24-48, 70 and 72-85, drawn to pyrimidines. In correspondence with election of claims of Group II, Applicants amended claims 1, 3, 8, 9, 12, 13, 16, 28, 30, 35-37, 39, 44 and 70, and canceled claims 2, 19-23, 29, 71, and 86-94. In the Non-Final Office Action dated December 3, 2003, the Examiner rejected claims 1, 3-18, 24-28, 30-47, 70 and 72-85, objected to claims 4-15, 18, 26, 27 and 30-47, and pursuant to election requirement withdrew claims 48-69 from further consideration.

Currently, Applicants cancel claims 1, 3, 16, 17, 24, 25, 50, 51, 53, 55, 57, 58, 74-75, and 82-85, amend claims 4, 8, 9, 12, 18, 26, 28, 35, 36, 48, 70, 72, 73, 76, 77, and 79, and add new claims 95-101. By this amendment, claims 4, 8, 9, 12, 18 and 26 are made independent and they incorporate all limitations of the claims on which they used to depend. Claims 8, 9, 28, 35, 36 and 70 have been amended to address formal claim drafting requirements. No new matter has been added by the present amendment. The claims now pending in the application are: 4-15, 18, 26-28, 30-47, 48, 49, 52, 54, 56, 59-69, 70, 72, 73, 76, 77, 79, and 95-101. The Examiner's rejections and objections are addressed below.

Election/Restriction Requirement

Applicants thank Examiner for indication that the claims of Group V (claims 48-69), drawn to pharmaceutical compositions comprising a compound according to claims 1 and 28 and an additional active ingredient, would be rejoined and examined if the claims of Group II (claims 1-18, 24-48, 70 and 72-85), drawn to pyrimidines, were found to be allowable. Since Applicants believe that the present amendment of claims of Group II places those claims in condition for allowance, Applicants also amend claim 48 to make claims of Group V properly dependent on amended claims of Group II. Further examination of claims of Group V is requested.

Substitute Specification

Pursuant to Examiner's requirement under 37 CFR §1.125(b) and (c), Applicants enclose herein a Substitute Specification in clean and marked versions.

In the course of inspection of the application, Applicants have discovered that some text and table pages 148 to 206 of the parent PCT application did not get carried over into the instant continuation filed January 14, 2002. The continuation incorporates the earlier PCT/US00/19185 application by reference.

Therefore, Applicants hereby submit a Substitute Specification in clean and marked versions incorporating left out text of the parent PCT application. The Substitute Specification also includes structures from pages 148 to 206 of the PCT application. The single structure on page 163 of the continuation as filed (the last page of the table) was the first structure on page 148 of the PCT application. It should be noted that the originally filed tables listed molecular weights of displayed chemical structures while all table pages in the Substitute Specification show identifier numbers for the chemical structures instead of molecular weights. Since it would be awkward to show strikethroughs and underlinings for deleted and added text inside of the tables, Applicants ask Examiner to note and accept this amendment.

Applicants have included with this response a declaration by the practitioner that the material in the Substitute Specification is the same material incorporated by reference [see MPEP §608.01(p)].

Per verbal agreement reached in a telephone call to Examiner on April 20, 2004, the added table pages in the Substitute Specification do not have underlining markings since the added pages bear only tables, which would be awkward to underline. Applicants present that therefore, the Substitute Specification submission requirements have been met to the best of Applicants' ability. Furthermore, Applicants are willing to take any additional measures that may be suggested by the Examiner to address this requirement.

Rejection under 35 U.S.C. §112, second paragraph

Claims 1, 3-18, 24-28, 30-47, 70, and 72-85 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention.

Specifically, claims 1 and 28 were found to be indefinite as to the definition of A^1 and W. The remainder of claims rejected under 35 U.S.C. §112, second paragraph, were rejected as being dependent on a rejected claim. By this amendment, claim 1 is being canceled and claim 28 is being amended to address Examiner's rejection. Furthermore, Applicants' amendments to claims 8, 9, 35, 36 and 70 correct similar indefiniteness issues. Thus, Applicants respectfully submit that the rejection of claims 1 and 28 under 35 U.S.C. §112, second paragraph, is overcome by the present amendments.

The Examiner also rejected claims 70, 72 –75, and 82-84 as being indefinite by reciting the term "inappropriate". Without acceding to the propriety of the Examiner's position, and in order to expedite prosecution, Applicants have amended claims 70 and 72, and canceled claims 74, 75, and 82-84. Accordingly, Applicants believe that this rejection has now been rendered moot and request that such rejection be withdrawn.

Rejection under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 70 and 72-85 under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for treating vasculopathy and asthma, does not provide enablement for any or all bradykinin mediated conditions.

Applicants thank the Examiner for acknowledging utility and enablement of methods of treatment of vasculopathy and asthma. Furthermore, without acceding to the propriety of the Examiner's position, and in order to expedite prosecution, Applicants have amended claims 70, 72, 73, 76, 77 and 79, and added new claims 95-101. The amended and new claims are directed to methods of treatment of specific recited disorders previously claimed in a dependent form in claims 72-84. Applicants also would like to point out that the new claim 95, directed to methods of treatment of hypertensive vasculopathy, is supported by the specification on page 2, lines 12-13. Therefore, no new matter has been added by this amendment.

The amended and new claims have utility and are enabled as supported by the attached Affidavit of Dr. Maria L. Webb. In her Affidavit, Dr. Webb states that as a person of skill in the art, she would accept the disclosures of the results *in vitro* presented in the application as predictive of utility for treatment of inflammation (including inflammation associated with edema, rhinitis, septic shock, multiple sclerosis, atherosclerosis, Alzheimer's

disease, and closed head trauma), pain (including pain associated with inflammation, chronic pain, and dental pain), hyperalgesia, post-capillary resistance, diabetic symptoms associated with insulitis (such as hyperglycemia, diuresis, proteinuria, and increased nitrile and kallikrein urinary tract excretion), and edema.

In addition, in her Affidavit, Dr. Webb states as a person of skill in the art, that it would have been within the ordinary skill in the art to generate pharmaceutical dosages of the Bradykinin B1 receptor antagonists disclosed in the present application to be used in methods of treatment of above-mentioned disorders and that such dosing could be done as a matter of routine and without undue experimentation.

In her analysis, Dr. Webb relies on her knowledge and skill in the art and on numerous cited scientific publications.

Furthermore, claims 74-75, 82-85 have been cancelled. Thus, claim 85 directed to methods for stimulating hair growth or preventing hair loss is no longer before the Examiner.

Therefore, Applicants believe that this rejection has now been rendered moot and request that such rejection be withdrawn.

Rejection under 35 U.S.C. §103

The Examiner rejected claims 1, 3, 16, 17, 24 and 25 under 35 U.S.C. §103(a) as being unpatentable over Arnaitz et al., WO 98/37079. Without acceding to the propriety of the Examiner's position, and in order to expedite prosecution, Applicants have canceled claims 1, 3, 16, 17, 24 and 25. Claims 4, 8, 9, 12, 18 and 26 have been amended to make them independent and incorporating all limitations of the canceled claims on which they used to depend.

Accordingly, Applicants believe that this rejection has now been rendered moot and request that such rejection be withdrawn.

Objection and Allowable Subject Matter

The Examiner objected to claims 4-15, 18, 26-27, and 30-47 as depending on the rejected base claim. Applicants thank Examiner for pointing out that these claims would be

allowable if they did not depend on the rejected base claim. By this amendment, claims 4, 8, 9, 12, 18 and 26 are made independent and they incorporate all limitations of the claims on which they used to depend. Claims 8, 9, 28, 35, 36 and 70 have been amended to address formal claim drafting requirements. Therefore, Applicants respectfully request withdrawal of this objection.

Although the Examiner did not indicate that claim 28 is allowable, the only rejection addressed to this claim was based on 35 U.S.C. §112, second paragraph, indefiniteness grounds. Since claim 28 was amended to overcome this rejection, it is believed that claim 28 is allowable.

Conclusion

Reconsideration and further examination is respectfully requested.

Applicants have made a diligent effort to place the claims in condition for allowance. However, should there remain unresolved issues that require adverse action, it is respectfully requested that the Examiner telephone Edward Timmer, Applicants' Attorney at (518) 452-5600 so that such issues may be resolved as expeditiously as possible.

For these reasons, and in view of the above amendments, this application is now considered to be in condition for allowance and such action is earnestly solicited.

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to:

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Date of Deposit: May 3, 2004

Edward Timmer
EDWARD TIMMER

Respectfully submitted,

Edward Timmer
EDWARD TIMMER
Attorney for Applicant(s)
USPTO Registration Number 46,248

Dated: May 3, 2004

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SUBSTITUTE SPECIFICATION

Copy with Markings

1.14 BRADYKININ B_1 RECEPTOR ANTAGONISTS

Cross Reference to Related Applications

This application is a continuation of PCT application PCT/US00/19185 filed July 14, 2000, and published under PCT Article 21(2) in English as WO 01/05783 on January 25, 2001. PCT/US00/19185 claimed the priority of US provisional application 60/143,990, filed July 15, 1999. The entire disclosures of both are incorporated herein by reference.

Field of the Invention

The invention relates to pyrimidines, triazines, and anilines that are bradykinin B_1-receptor antagonists. The compounds are useful for treating diseases associated with inappropriate or excessive bradykinin receptor activity, such as diabetic vasculopathy, inflammation, pain, hyperalgesia, asthma, rhinitis, septic shock, atherosclerosis and multiple sclerosis.

Background of the Invention

Bradykinin receptors of two classes are known. The B_1 receptor (B_1-BK) is not present in normal cells under normal conditions. In contrast, the B_2-BK receptor is normally present on many cell types or tissues. Although the B_1 receptor (B_1-BK) is not present under normal conditions, its synthesis is induced in blood vessel muscular layers during inflammation.

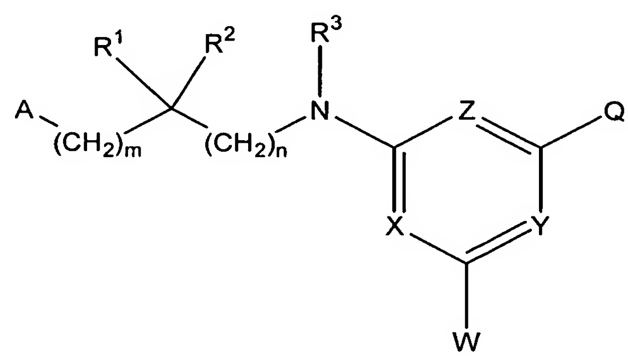
Recent reports point to an important role of bradykinin B_1 receptors in physiopathology. Dray and Perkins [Trends in Neurosci. 16, 99-104(1993)] have reviewed the possible implication of B_1 receptors in various inflammatory states, in tissue reactions and in hyperalgesia. Alvarez et al. [Clin. Sci.82, 513-519 (1992)]

have provided evidence that B_1 receptors are present in spontaneously hypertensive rats (SHR), and Regoli et al. [PCT application WO 98/07746] have provided evidence that inappropriate B_1 receptor activity is associated with some forms of diabetes. In particular, it is known that capillary permeability is augmented in the streptozotocin diabetic rat model, and the vascular BK receptors of the portal veins of these animals have been shown to exhibit enhanced contractibility and capillary permeability in response to the B_1-agonist desArg^{8}BK. This effect was abolished by the B_1-antagonist Lys[Leu]desArg^{9}BK while the B_2-antagonist HOE140 had no effect. A similar increased sensitivity to desArg^{9}BK was observed in untreated SHR animals, prior to the establishment of hypertension, which was reversed by the same B_1-antagonist. These results indicate that the B_1-receptor is a target for a drug-preventive approach to diabetic or hypertensive vasculopathy.

Peptide antagonists of bradykinin receptors are known, although most reported antagonists have activity towards B_2-receptors. There are to date very few small molecule B_1 antagonists. It would be useful to have effective antagonists of the B_1-BK receptor.

Summary of the Invention

In one aspect, the invention relates to a genus of bradykinin B_1 receptor antagonists sharing the general formula I:



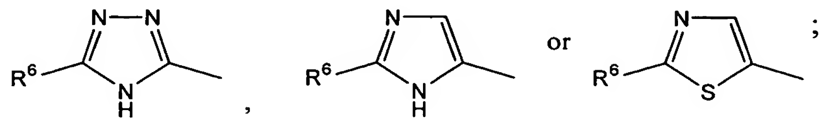
I

wherein:

(a) all of X, Y and Z are CH; or (b) one of X, Y and Z is N and the rest of X, Y and Z are CH; or (c) two of X, Y and Z are N and the other of X, Y and Z is CH; or (d) all of X, Y and Z are N;

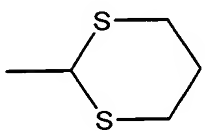
A is A^1 or A^2;

A^1 is $R^4R^5N\text{-}C(O)\text{-}$



A^2 is chosen from $R^7C(O)NH\text{-}$, $R^7S(O)_2NH\text{-}$, $R^4NH\text{-}$, and $R^4O\text{-}$;

Q is chosen from heteroaryl, aryl, $\text{-}CH_2R^{13}$, $\text{-}CH{=}N\text{-}OCH_3$ and

 ;

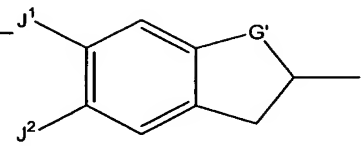
W is chosen from H, Cl, F, R^8, C_1-C_4-alkylaryl, $\text{-}OR^8$, $\text{-}SR^8$, $\text{-}NR^9R^{10}$ and $\text{-}NHC(O)R^{11}$;

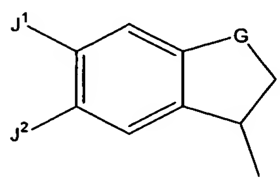
R^1 is chosen from alkyl, cycloalkyl, alkenyl, C_1-C_3-alkylcycloalkyl, heterocyclyl, C_1-C_3-alkylheterocyclyl, aryl, C_1-C_3-alkylaryl, heteroaryl, C_1-C_3-alkylheteroaryl, (C_1-C_3-alkyloxy)alkyl, (C_1-C_3-alkyloxy)cycloalkyl, (C_1-C_3-alkylthio)alkyl, (C_1-C_3-alkylthio)cycloalkyl and (C_1-C_3-alkylsulfonyl)alkyl;

R^2 is H or C_1-C_3-alkyl, or R^1 and R^2 taken together form a 5- to 7-membered ring structure optionally containing O, S or NR^{12};

R^3 is H or C_1-C_6-alkyl, or, when n is zero, R^2 and R^3 taken together may form a 6-membered ring, which may be fused to a six-membered saturated or aromatic carbocycle;

R^4 is chosen from H, aryl, heteroaryl, ~~C_1-C_4-alkylaryl and C_1-C_4-alkylheteroaryl~~, $\underline{C_1\text{-}C_4\text{-alkyl substituted with from one to three aryl}}$

or heteroaryl residues,  and

 , wherein J^1 and J^2 are independently chosen from H, F, Cl, CN, NO_2 and CH_3,; G is chosen from $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-OCH_2-$, $-CH_2O-$, $-CH_2CH_2O-$, $-OCH_2CH_2-$, -O-, -N(lower alkyl)-, -N(lower alkyl)CH_2-, $-CH_2$N(lower alkyl)-, -S-, -SO-, $-SO_2-$, $-CH_2S-$, $-SCH_2-$, $-CH_2SO-$, $-SOCH_2-$, $-CH_2SO_2-$, and $-SO_2CH_2-$; and G' is chosen from $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-OCH_2-$, $-OCH_2CH_2-$, -N(lower alkyl)CH_2-, $-SCH_2-$, $-SOCH_2-$ and $-SO_2CH_2-$;

R^5 is H or C_1-C_3-alkyl, with the proviso that both R^3 and R^5 cannot be alkyl;

R^6 is aryl;

R^7 is aryl or C_1-C_3-alkylaryl;

R^8 is chosen from alkyl, aryl, heteroaryl, substituted alkyl, C_1-C_4-alkylaryl, C_1-C_4-alkylheterocyclyl and C_1-C_4-alkylheteroaryl;

R^9 is chosen from H, alkyl, alkenyl, substituted alkyl, cycloalkyl, aryl, alkoxy, heteroaryl, fluoroalkyl, C_1-C_4-alkylcycloalkyl, (C_1-C_4-alkoxy)alkyl, (C_1-C_4-alkoxycarbonyl)alkyl, (C_1-C_4-alkylthio)alkyl, heterocyclyl, C_1-C_4-alkylheterocyclyl, C_1-C_4-alkylaryl, and C_1-C_4-alkylheteroaryl;

R^{10} is H or C_1-C_3-alkyl, or

R^9 and R^{10} taken together may form a 5- to 7-membered ring structure optionally containing O, S, SO, SO_2 or NR^{12}, said ring optionally substituted

with -OH, -CN, -COOH or -$COOCH_3$;

R^{11} is aryl;

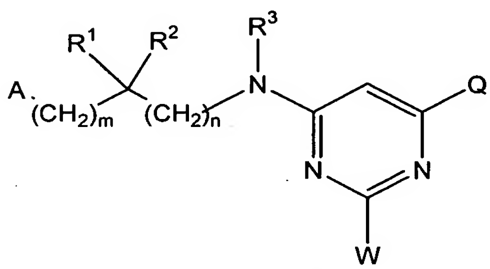
R^{12} is chosen from H, C_1-C_3-alkyl, alkoxycarbonyl, methoxyacetyl and aryl;

R^{13} is chosen from -OH, -OTHP, 1-imidazolyl, and 1-pyrrolyl;

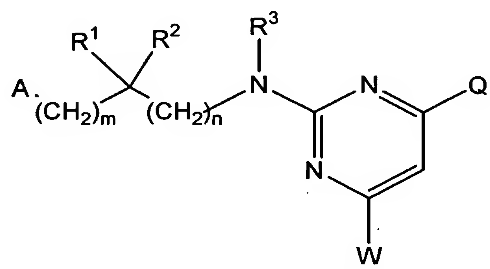
m is zero or one; and

n is zero or one, with the proviso that when A is A^2, m and n cannot both be zero.

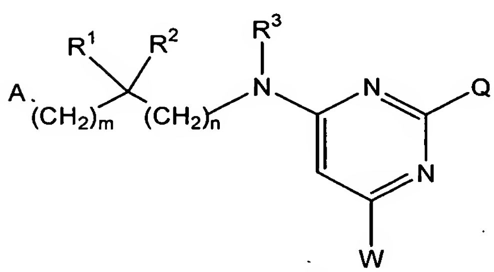
This genus may be considered to comprise subgenera of pyrimidines (IIa-IIc), triazines (III), anilines (IV) and pyridines (not shown):



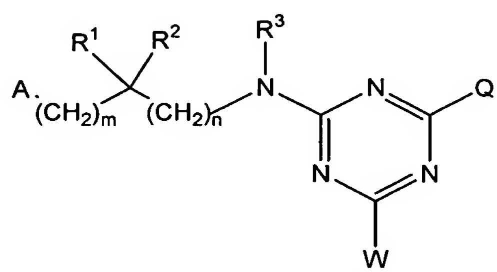
IIa



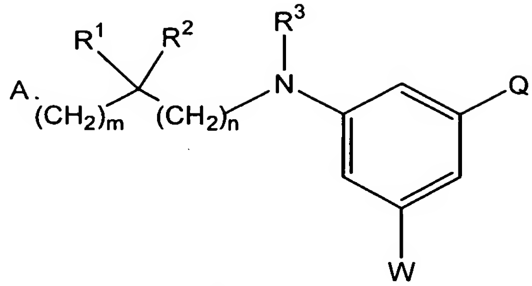
IIb



IIc



III



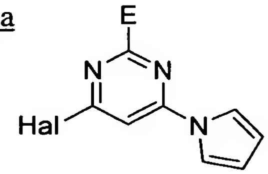
IV

In another aspect, the invention relates to a method of treating a condition resulting from inappropriate bradykinin receptor activity comprising administering to a subject in need of such treatment a therapeutically effective amount of a compound of formula I. Conditions resulting from inappropriate bradykinin receptor activity include diabetic vasculopathy, post-capillary resistance or diabetic symptoms associated with insulitis, inflammation, edema, liver disease, asthma, rhinitis, septic shock, pain, hyperalgesia, multiple sclerosis, atherosclerosis, Alzheimer's disease or closed head trauma. Of particular importance are chronic pain, pain associated with inflammation and dental pain. Diabetic symptoms associated with insulitis include hyperglycemia, diuresis, proteinuria and increased nitrite and kallikrein urinary excretion. Stimulating hair growth or preventing hair loss may also be accomplished by administering to a subject in need of such treatment a therapeutically effective amount of a compound of formula I.

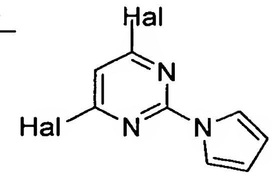
~~In other aspect, the invention relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and compounds of formula I.~~

In another aspect, the invention relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and compounds of formula I. The formulations may additionally comprise steroidal or nonsteroidal anti-inflammatory drugs (NSAIDS), cyclo-oxygenase (COX) inhibitors or selective cyclooxygenase-2 (COX-2) inhibitors.

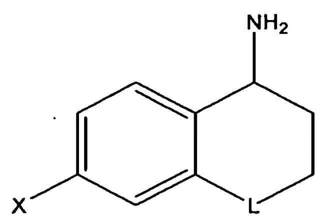
In another aspect, the invention relates to compounds, useful as intermediates in the synthesis of bradykinin inhibitors. One genus of such compounds is represented by formula



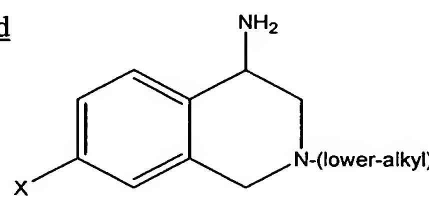
or



wherein E is halogen or methylthio and Hal is halogen. Another genus is represented by formulae



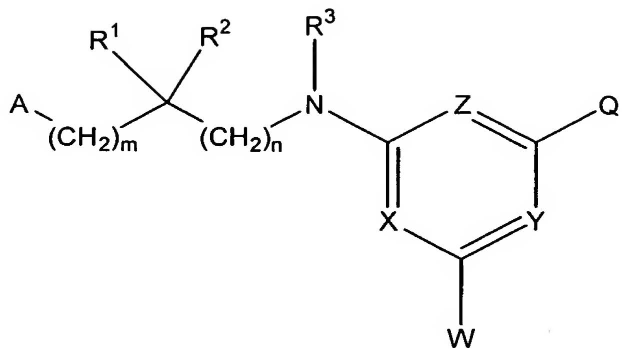
and



wherein X is -CN or halogen and L is -O-, $-CH_2-$ or $-N(CH_3)-$.

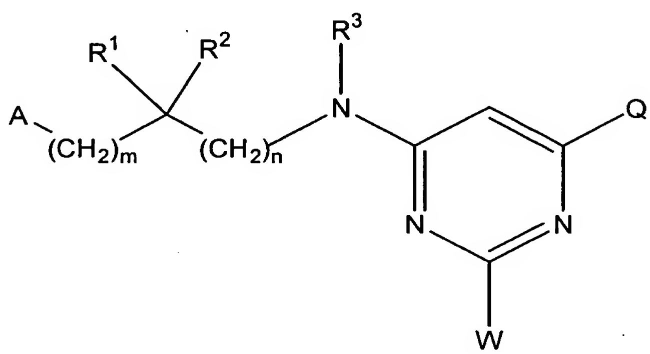
Detailed Description of the Invention

Preferred compounds of the invention are found in the class of pyrimidines of formula II

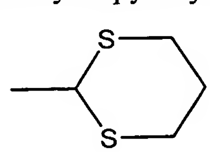


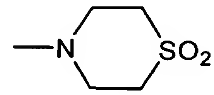
II

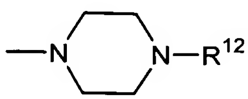
These are compounds of formula I in which two of X, Y and Z are N and the third is CH. Three classes of pyrimidines can be limned, depending on which of X, Y and Z is CH The first of these is the 4-pyrimidinamines, in which Z is CH. These have the formula IIa

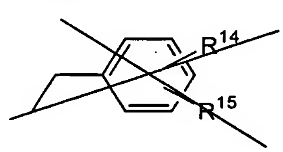
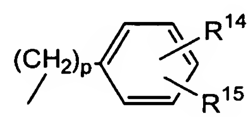
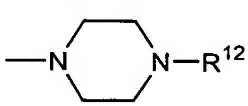


IIa

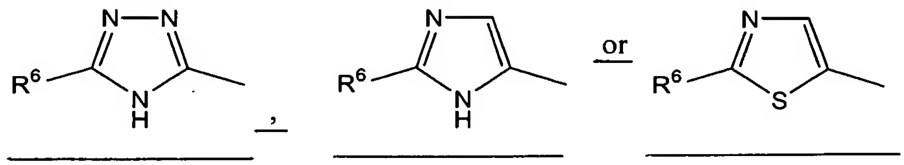
In preferred embodiments, Q is chosen from imidazolyl, methylimidazolyl, pyrrolyl, methylpyrrolyl, pyrazolyl, methylpyrazolyl, hydroxymethylimidazolyl, (dimethylaminomethyl)imidazolyl, furanyl, methylfuranyl, thienyl, oxazolyl, thiazolyl, pyridinyl, quinolinyl, 1-methylpyrimidin-2-onyl, phenyl, fluorophenyl, hydroxymethyl, tetrahydropyranyloxymethyl, imidazolylmethyl, pyrrolylmethyl, -CH=N-OCH$_3$ and  .

In particularly preferred embodiments Q is pyrrol-1-yl, imidazol-1-yl, furan-3-yl, 2-methylimidazol-1-yl or 4-methylimidazol-1-yl; A is $R^4R^5N\text{-}C(O)\text{-}$; W is Cl, NHR^9, $N(CH_3)R^9$, OR^8, SR^8, R^8, morpholin-4-yl,  or

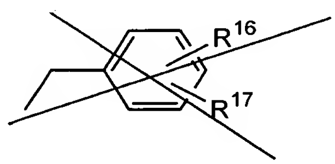
 ; R^1 is chosen from alkyl, cycloalkyl, C_1-C_3-alkylaryl, C_1-C_3-alkylcycloalkyl, C_1-C_3-alkylheterocyclyl, and C_1-C_3-alkylheteroaryl; R^2,R^3 and R^5 are H; R^4 is C_1-C_4-alkylaryl or C_1-C_4-alkylheteroaryl; R^8 is C_1-C_4-alkylaryl; R^9 is chosen from hydrogen, alkyl, ~~fluoroalkyl, cyanoalkyl, hydroxy- and dihydroxyalkyl, (C_1-C_4-alkoxy)alkyl, (C_1-C_4-alkylthio)alkyl,~~ substituted alkyl, (C_1-C_4)-alkoxy, C_1-C_4-alkylcycloalkyl, C_1-C_4-alkylaryl, heterocyclyl, C_1-C_4-alkylheteroaryl, and C_1-C_4-alkylheterocyclyl; and m and n are zero. When W is NHR^9 , preferred values of R^9 are hydrogen; methyl; ethyl; 2,2,2-trifluoroethyl; allyl; cyclopropyl; 2-cyanoethyl; propargyl; methoxy; methoxyethyl; cyclopropyl; cyclopropylmethyl; (methylthio)ethyl; 3-methoxypropyl; 3-pyridyl; 2-(3-pyridyl)ethyl; 2-(2-pyridyl)ethyl; 3-pyridylmethyl; 4-pyridylmethyl; 4-pyridylmethyl-N-oxide; 2-pyridazinylmethyl; sulfolan-3-yl; 3-tetrahydrofuranyl; 2-tetrahydrofuranylmethyl; 3-(1-imidazolyl)propyl; 1-*t*-butoxycarbonyl-4-piperidinyl; 1-*t*-butoxycarbonyl-4-piperidinylmethyl; 2-(hydroxyimino)propyl; 2-(methoxyimino)propyl; 2-oxo-1-propyl; and

  wherein R^{14} is H, Cl, F, CN, NO_2, SO_2NH_2, CF_3, $COOCH_3$, OCH_3, OH, SO_2CH_3, $N(CH_3)_2$ or COOH; R^{15} is chosen from H, OCH_3, F and Cl; and p is one or two. When W is  , R^{12} is preferably t-butoxycarbonyl, methoxyacetyl or phenyl.

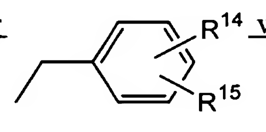
In another preferred embodiment of formula IIa, A is R^4~~R^5N-C(O)-;~~



and R^1 ~~chosen from~~ is n-butyl; cyclohexylmethyl; cyclopentylmethyl; 2-methylpropyl; 3-methyl-1-butyl; cyclohexyl; 2,2-dimethylpropyl; benzyl; 2-thienylmethyl; 1-*t*-butoxycarbonyl-4-piperidinyl; 4-chlorobenzyl; 2-pyranylmethyl; 4-pyranylmethyl; 4-pyranyl ~~and~~ or 1,1-dimethylethyl; R^2[[,]] and R^3 ~~and R^5~~ are H; ~~R4 is aryl, pyridinylmethyl, pyridinyl or~~



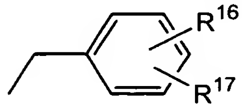
~~; R^{16} is H, F, Cl, CN, NO_2, SO_2NH_2, CF_3, CH_3, $COOCH_3$, OCH_3, SO_2CH_3, $N(CH_3)_2$ or COOH; and R^{17} is H, OCH_3 or Cl. In these compounds, the carbon to which R1 and R2 are attached is preferably of the R absolute configuration, i.e. derivatives of D-amino acids, when m and n are zero.~~ Q is imidazolyl or pyrrolyl; W is NHR^9; and R^9 is alkyl, cycloalkyl or



wherein R^{14} is chosen from H, Cl, F, CN, NO_2, SO_2NH_2, CF_3, $COOCH_3$, OCH_3, SO_2CH_3, $N(CH_3)_2$ and COOH; and R^{15} is chosen from H, OCH_3 and Cl.

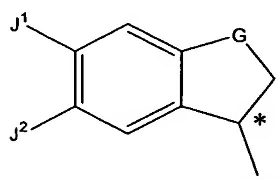
In another preferred embodiment of formula IIa, A is R^4R^5N-C(O)-; R^1 is chosen from isopropyl; n-butyl; cyclohexylmethyl; cyclopentylmethyl; naphthylmethyl; cyclohexylethyl; 2-methylpropyl; 3-methyl-1-butyl; cyclohexyl; 2,2-dimethylpropyl; benzyl; 2-thienylmethyl; 1-*t*-butoxycarbonyl-4-piperidinyl; 4-

methoxybenzyl; 4-chlorobenzyl; 3,4-dichlorobenzyl; 2-pyranylmethyl; 4-pyranylmethyl; 4-pyranyl and 1,1-dimethylethyl; R^2, R^3 and R^5 are H; R^4 is aryl (including substituted aryl), indanylmethyl, heteroarylmethyl, pyridinyl or



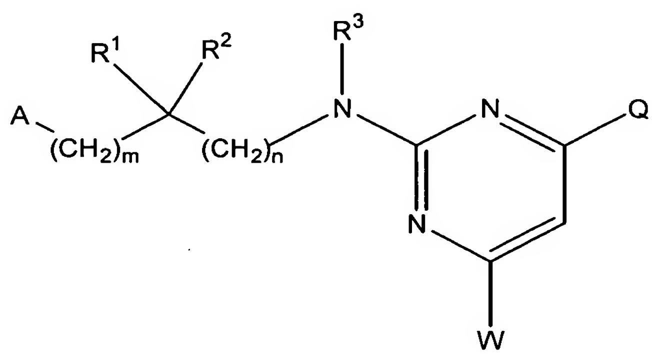
; R^{16} is H, F, Cl, CN, NO_2, SO_2NH_2, CF_3, CH_3, $COOCH_3$, OCH_3, SO_2CH_3, $SOCH_3$, $N(CH_3)_2$ or COOH; and R^{17} is H, OCH_3, F or Cl. In these compounds, the carbon to which R^1 and R^2 are attached is preferably of the R absolute configuration, i.e. derivatives of D-amino acids, when m and n are zero.

In another preferred embodiment of formula IIa, which is also a preferred embodiment in other subgenera of the general formula I, R^4 is



. In this genus, one of J^1 and J^2 is preferably H and the other is H, Cl or CN and G is chosen from $-CH_2-$, $-CH_2CH_2-$, $-OCH_2-$, -O- and $-CH_2N$(lower alkyl)-. Compounds having the R configuration at the carbon indicated with an asterisk have higher potency as bradykinin receptor antagonists.

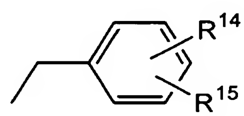
In a second class of pyrimidines, the 2-pyrimidinamines, Y is CH. These have the formula IIb:



IIb

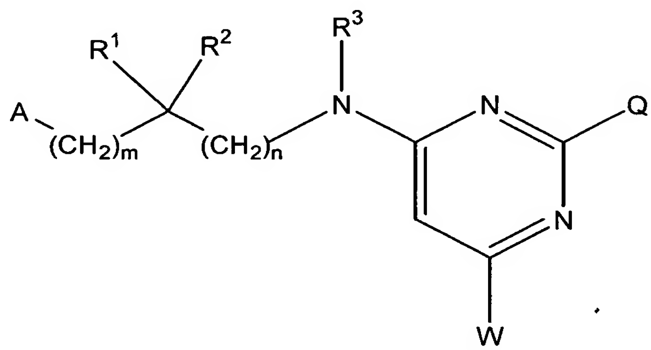
Preferred embodiments are as for IIa. Particularly preferred embodiments are those

in which Q is imidazolyl, pyrrolyl, pyridinyl, fluorophenyl or 2-thienyl. In these compounds, A is preferably R^4R^5N-C(O)-; W is H, Cl, NHR^9 or OR^8; R^1 is alkyl or C_1-C_3-alkylcycloalkyl; R^2, R^3 and R^5 are H; R^4 is C_1-C_4-alkylaryl or C_1-C_4-alkylheteroaryl; R^8 is C_1-C_4-alkylaryl; R^9 is hydrogen, alkyl, fluoroalkyl, (C_1-C_4-alkoxy)alkyl, (C_1-C_4-alkylthio)alkyl, C_1-C_4-alkylcycloalkyl, C_1-C_4-alkylaryl, heterocyclyl, C_1-C_4-alkylheteroaryl, or C_1-C_4-alkylheterocyclyl; and m and n are zero. Among these, the most preferred compounds are those in which W is NHR^9 and R^9 is



wherein R^{14} is H, F, Cl, CN, NO_2, SO_2NH_2, CF_3, $COOCH_3$, OCH_3, SO_2CH_3, $N(CH_3)_2$ or COOH; and R^{15} is H, OCH_3 or Cl.

In the third class of pyrimidines, a different set of 4-pyrimidinamines, X is CH. These have the formula IIc:

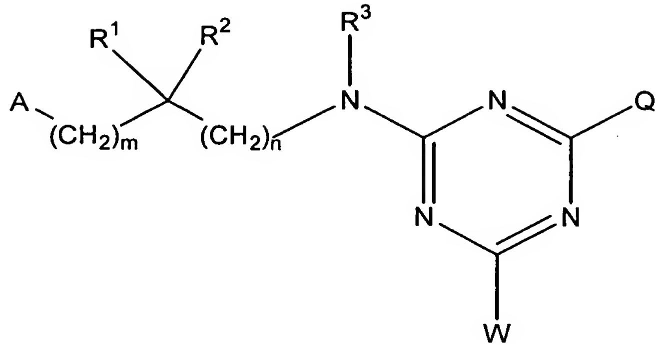


IIc

Preferred embodiments are as for IIa. Particularly preferred embodiments are those in which Q is imidazolyl or pyrrolyl <u>and m and n are zero</u>. In these compounds, A is preferably R^4R^5N-C(O)-; W is NHR^9; R^1 is cyclohexylmethyl; 2-methylpropyl or 3-methyl-1-butyl; R^2, R^3 and R^5 are H; and R^4 and R^9 are benzyl or substituted benzyl.

Triazines form another subgenus of the invention according to formula I; in this subgenus, all of X, Y, and Z are N. The triazines of interest have the formula

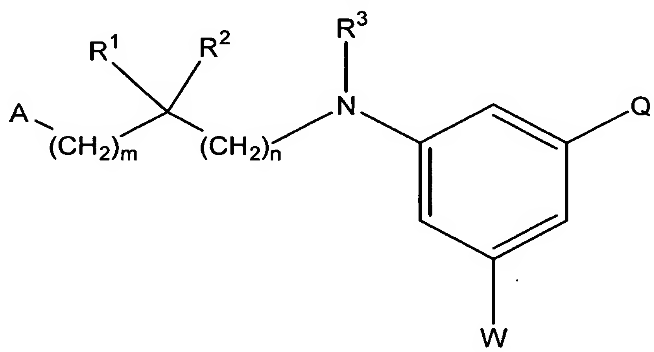
III



III

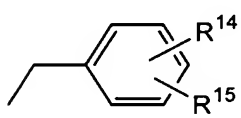
Preferred embodiments are as for the pyrimidines. Particularly preferred embodiments are those in which Q is imidazolyl or pyrrolyl. In these compounds, A is preferably $R^4R^5N\text{-}C(O)\text{-}$; W is NHR^9; R^1 is cyclohexylmethyl; 2-methylpropyl or 3-methyl-1-butyl; R^2, R^3 and R^5 are H; and R^4 and R^9 are benzyl or substituted benzyl.

Anilines form another subgenus of the invention according to formula I in which all of X, Y, and Z are CH. Anilines of the invention have the formula IV:



IV

Preferred embodiments are as for the pyrimidines. Particularly preferred embodiments are those in which Q is imidazolyl or pyrrolyl. In these compounds, A is preferably $R^4R^5N\text{-}C(O)\text{-}$; W is NHR^9; R^1 is alkyl, cycloalkyl, C_1-C_3-alkylaryl or C_1-C_3-alkylcycloalkyl; R^2, R^3 and R^5 are H; R^4 is C_1-C_4-alkylaryl; R^9 is



; R^{14} is H, Cl, CN, NO_2, SO_2NH_2, CF_3, $COOCH_3$, OCH_3,

SO_2CH_3, $N(CH_3)_2$ or COOH; R^{15} is H, OCH_3 or Cl; and m and n are zero.

All of the compounds falling within the foregoing parent genus and its subgenera are useful as bradykinin inhibitors, but not all the compounds are novel. In particular, certain pyrimidines in which Q is imidazolyl and W is H, Cl, F or lower alkyl are disclosed as inhibitors of nitric oxide synthetase in PCT application WO 98/37079. The specific exceptions in the claims below reflect applicants' intent to avoid claiming subject matter that, while functionally part of their invention, is not patentable to them for reasons having nothing to do with the scope of the inventive concept.

"Alkyl" is intended to include linear, or branched hydrocarbon structures and combinations thereof; hydrocarbons of 20 or fewer carbons are generally preferred. "Lower alkyl" means alkyl groups of from 1 to 6 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, s- and t-butyl, pentyl, hexyl, and the like.

"Cycloalkyl" includes cycloalkyl groups of from 3 to 12 carbon atoms. Examples of "cycloalkyl" groups include c-propyl, c-butyl, c-pentyl, c-hexyl, 2-methylcyclopropyl, cyclopropylmethyl, cyclopentylmethyl, norbornyl, adamantyl, myrtanyl and the like.

"Alkenyl" refers to a C_2 to C_{20} hydrocarbon of a linear, branched, or cyclic (C_5-C_6) configuration, and combinations thereof, having one or two degrees of unsaturation. C_2-C_8 Alkenes are preferred. Examples of alkenyl groups include vinyl, allyl, isopropenyl, pentenyl, hexenyl, c-hexenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, 2,4-hexadienyl and the like.

Alkynyl is C_2-C_8 alkynyl of a linear or branched configuration and combinations thereof. Examples of alkynyl groups include ethyne, propyne,

butyne, pentyne, 3-methyl-1-butyne, 3,3-dimethyl-1-butyne, and the like.

C_1 to C_{20} Hydrocarbon includes alkyl, cycloalkyl, alkenyl, alkynyl, aryl and combinations thereof. Examples include phenethyl, cyclohexylmethyl and naphthylethyl.

"Alkoxy" means alkoxy groups of from 1 to ~~6~~ 8 carbon atoms of a straight, branched, cyclic configuration and combinations thereof. Examples of alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like. Lower-alkoxy refers to groups containing one to four carbons.

Halogen includes F, Cl, Br, and I, with F and Cl as the preferred groups. "Halophenyl" means phenyl substituted by 1-5 halogen atoms. Halophenyl includes pentachlorophenyl, pentafluorophenyl, and 2,4,6-trichlorophenyl. "Fluoroalkyl" refers to an alkyl residue in which one or more hydrogen atoms are replaced with F, for example: trifluoromethyl, difluoromethyl, and pentafluoroethyl, 2,2,2-trifluoroethyl.

"Aryl" and "heteroaryl" mean a 5- or 6-membered aromatic or heteroaromatic ring containing 0-3 heteroatoms selected from O, N, and S; a bicyclic 9- or 10-membered aromatic or heteroaromatic ring system containing 0-3 heteroatoms selected from O, N, and S; or tricyclic 13- or 14-membered aromatic or heteroaromatic ring system containing 0-3 heteroatoms selected from O, N, and S; each of which rings is optionally substituted with up to three substituents chosen independently from lower alkyl, =O, nitro, halogen, hydroxy, alkoxy, alkylsulfonyl; methylenedioxy, alkoxyethoxy, cyano, amino, alkylamino, dialkylamino, acylamino, aminosulfonyl, C_1-C_6-alkoxycarbonyl, carboxy, methylsulfonamido, perfluoroalkyl, phenyl, benzyl, trityl, and phenoxy. 6- to 14-Membered aryl residues include, for example, benzene and naphthalene, and the 5- to 10-membered heteroaryl residues include, for example, imidazole, pyridine, indole,

oxazole, thiophene, benzopyranone, benzodioxan, benzodioxole, thiazole, furan, benzimidazole, quinoline, isoquinoline, quinoxaline, pyrimidine, pyrimidinone, pyridazine, tetrazole, and pyrazole. From the exemplary heteroaryl residues, it will be understood that heteroaryl does not imply the highest possible degree of unsaturation, only that there be at least one fully aromatic ring (e.g. benzodioxan).

"Arylalkyl" and "alkylaryl" denote an aryl residue attached to the parent structure through an alkyl residue. The alkyl need not be straight chain. Examples include benzyl, phenethyl, 2-phenylpropyl, 4-chlorobenzyl, and the like. The alkyl may also be a fused cycloalkyl such as indan (e.g.indan-2-yl), tetralin, and fluorene (e.g fluoren-9-yl) or a substituted alkyl, such as in 1-hydroxyindan-2-yl. "Heteroarylalkyl" denotes a residue comprising an alkyl attached to a heteroaryl ring such as pyridinylmethyl, pyrimidinylethyl, and the like.

"Heterocycloalkyl" means a cycloalkyl where one to three carbon atoms is replaced with a heteroatom, such as O, NR (R= H, alkyl), N→O, S, SO, SO_2 and the like. The term includes residues in which one or more rings is optionally substituted with up to three substituents chosen independently from lower alkyl, =O, halogen, hydroxy, alkoxy, amino, alkylamino, dialkylamino, acylamino, aminosulfonyl, C_1-C_6-alkoxycarbonyl, carboxy, methylsulfonamido, perfluoroalkyl, phenyl, benzyl, trityl, and phenoxy. When two heteroatoms are separated by a single carbon, the resulting heterocycloalkyls tend to be unstable in aqueous solutions and are therefore not preferred. Examples of heterocycloalkyls include: tetrahydrofuran, tetrahydropyran, piperidine, pyridine-N-oxide, 2-methyl-1,3-dithiane, dioxane, and the like.

"Substituted" alkyl, alkenyl, cycloalkyl, aryl, heteroaryl or heterocycloalkyl means alkyl, alkenyl, cycloalkyl, aryl, heteroaryl or heterocycloalkyl, wherein hydrogen atoms are replaced by halogen, hydroxy, hydroxyimino, alkoxyimino, nitro, alkoxy, ~~methylenedioxy,~~ alkoxyethoxy, amino, alkylamino, dialkylamino,

~~acylamino,~~ aminosulfonyl, ~~C_1-C_6-alkoxycarbonyl,~~ ~~methylsulfonamido,~~ ~~methylsulfonyl, methylthio,~~ perfluoroalkyl, phenyl, benzyl, trityl, phenoxy, amidino, guanidino, ureido, alkyl, alkylenedioxy (e.g. methylenedioxy), fluoroalkyl, carboxy (-COOH), carboalkoxy (i.e. acyloxy RCOO-), carboxyalkyl (i.e. alkoxycarbonyl -COOR), carboxamido (-$CONH_2$), acylamino (RCONH-), cyano, carbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, arylthio, arylsulfinyl, arylsulfonyl, arylsulfonamido, heteroaryl, heterocyclyl, phenoxy, ~~and~~ benzyloxy, or heteroaryloxy.

Most of the compounds described herein contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present invention is meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (R)- and (S)- isomers are prepared as described below using chiral synthons or chiral reagents, or resolved using conventional techniques. When a specific chirality is intended, it is indicated by the conventional wedge and dash notation; a simple single bond emanating from a chiral center implies no particular stereochemistry. Usually such compositions will be mixtures of enantiomers. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

As stated above, pharmaceutical compositions comprise a pharmaceutically acceptable carrier and compounds of formula I. The formulations may additionally include steroidal or nonsteroidal anti-inflammatory drugs (NSAIDS), cyclo-oxygenase (COX) inhibitors or selective cyclooxygenase-2 (COX-2) inhibitors. Preferred drugs for inclusion in pharmaceutical formulations include: NSAIDs such as arylpropionic acids, arylacetic acids, arylbutyric acids, fenamic acids,

arylcarboxylic acids, pyrazoles, pyrazolones, salicylic acids; and oxicams; cyclooxygenase inhibitors such as ibuprofen and salicylic acid derivatives; selective cyclooxygenase-2 inhibitors such as rofecoxib and celecoxib; steroidal antiinflammatory drugs such as finasteride, beclomethasone and hydrocortisone.

Abbreviations and Definitions

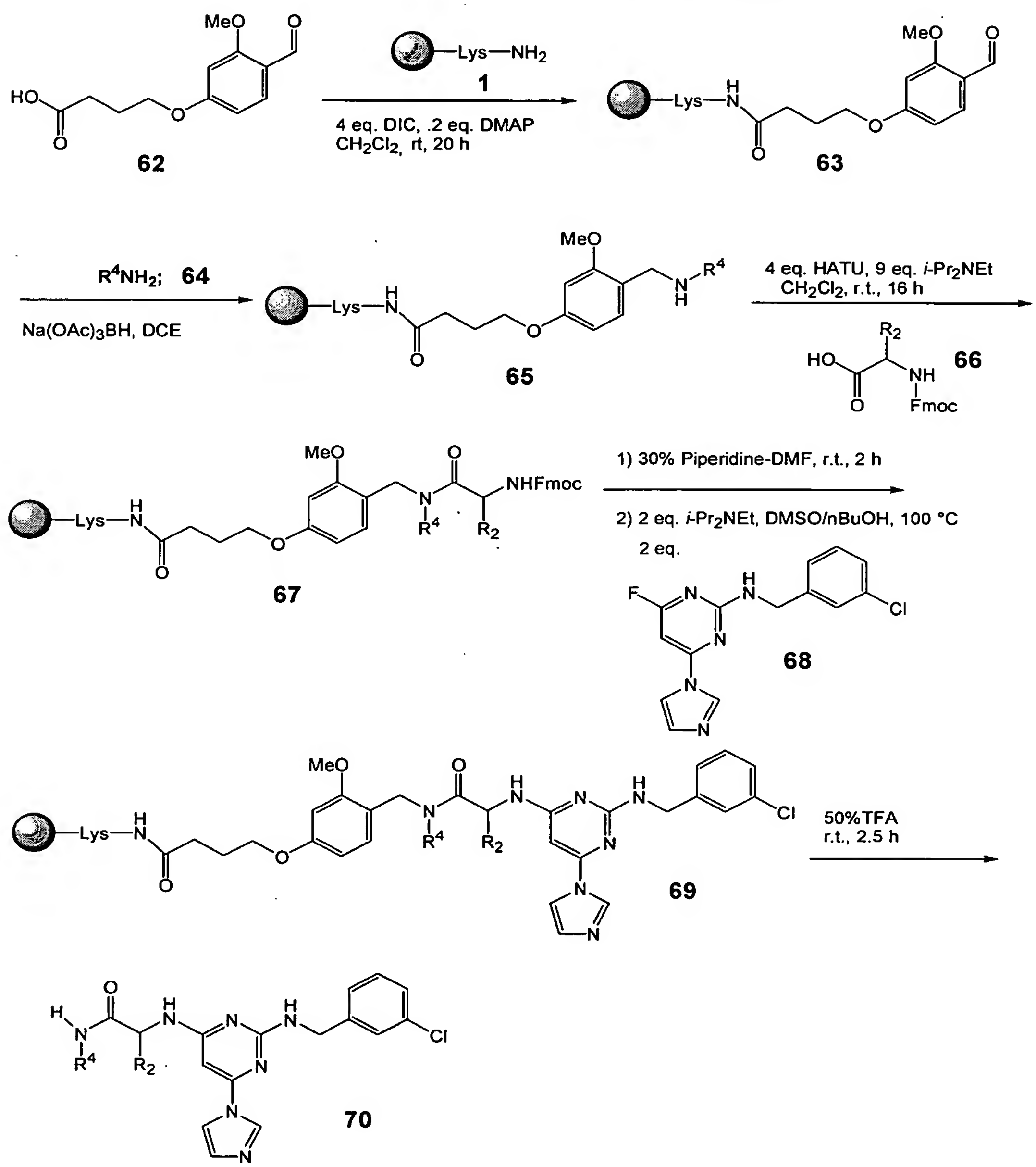
The following abbreviations and terms have the indicated meanings throughout:

Ac	=	acetyl
BNB	=	4-bromomethyl-3-nitrobenzoic acid
Boc	=	t-butyloxy carbonyl
Bu	=	butyl
c-	=	cyclo
DBU	=	diazabicyclo[5.4.0]undec-7-ene
DCM	=	dichloromethane = methylene chloride = CH_2Cl_2
DEAD	=	diethyl azodicarboxylate
DIC	=	diisopropylcarbodiimide
DIEA	=	N,N-diisopropylethyl amine
DMAP	=	4-N,N-dimethylaminopyridine
DMF	=	N,N-dimethylformamide
DMSO	=	dimethyl sulfoxide
DVB	=	1,4-divinylbenzene
EEDQ	=	2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
Fmoc	=	9-fluorenylmethoxycarbonyl
GC	=	gas chromatography
HATU	=	O-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HOAc	=	acetic acid
HOBt	=	hydroxybenzotriazole

Me	=	methyl
mesyl	=	methanesulfonyl
MTBE	=	methyl t-butyl ether
NMO	=	N-methylmorpholine oxide
PEG	=	polyethylene glycol
Ph	=	phenyl
PhOH	=	phenol
PfP	=	pentafluorophenol
PPTS	=	pyridinium p-toluenesulfonate
PyBroP	=	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
rt or RT	=	room temperature
sat'd or sat.	=	saturated
s-	=	secondary
t-	=	tertiary
TBDMS	=	t-butyldimethylsilyl
TFA	=	trifluoroacetic acid
THF	=	tetrahydrofuran
TMOF	=	trimethyl orthoformate
TMS	=	trimethylsilyl
tosyl	=	p-toluenesulfonyl
Trt	=	triphenylmethyl

The compounds of the invention are synthesized as follows.

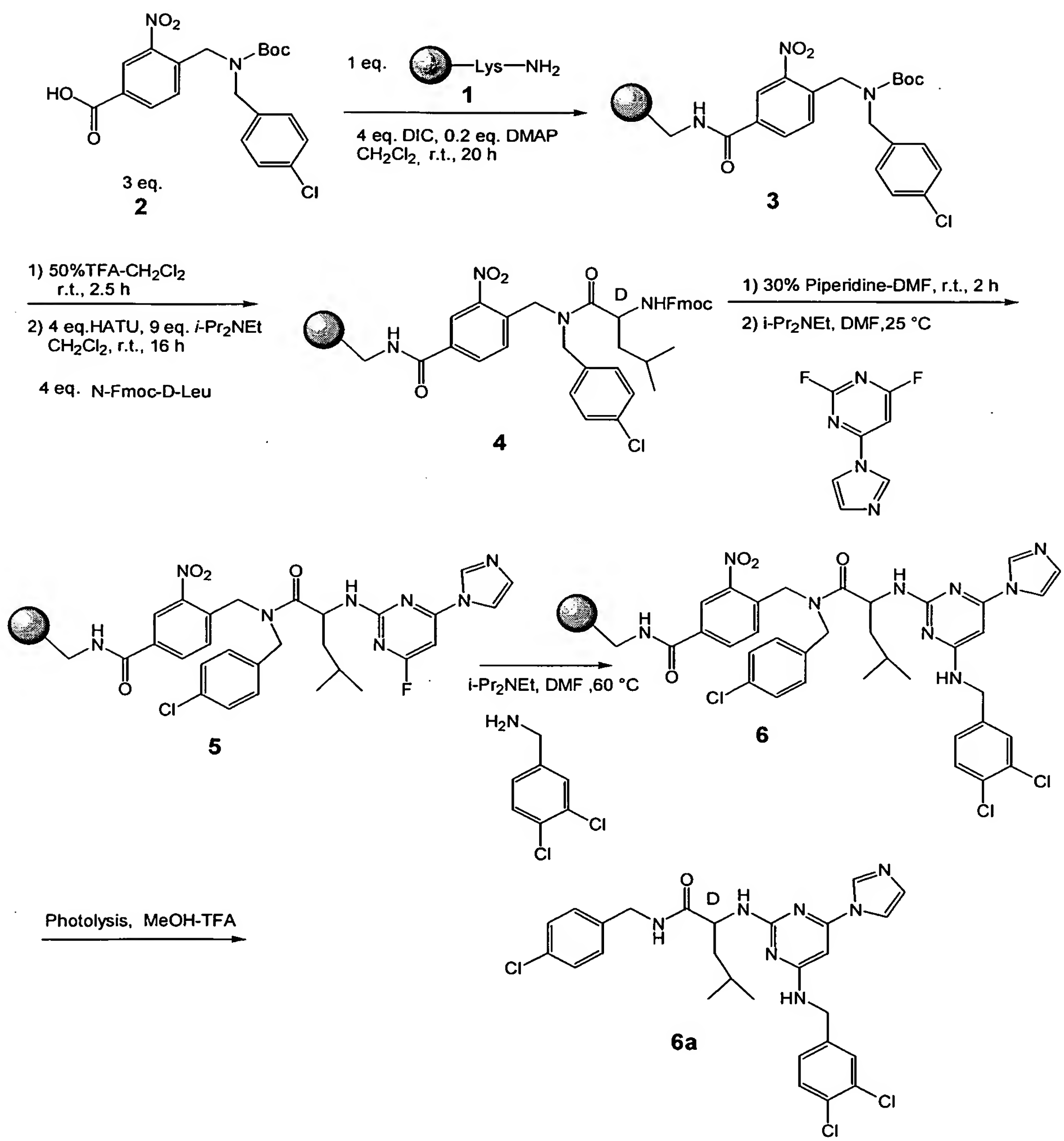
Scheme 1 Generic Solid Phase Synthesis



Amino functionalized TentaGel resin **1** (10 g 5.2 mmole) was suspended in 50 mL of CH_2Cl_2 and treated with 3.73 g of linker acid **62** (15.6 mmole), 3.25 mL of DIC (20.8 mmole), and 63 mg of DMAP (0.52 mmole). After 48h at room temperature, 3.77g of linker acid **62,** 3.25 mL of DIC and 2.1g HOBt were added. The mixture was shaken at room temperature for 17 h and then washed with DMF twice, CH_2Cl_2 ten times to give resin **63**. The resins **63** was treated with amine R^4NH_2 **64** and $Na(OAc)_3BH$ in dichloroethane at room temperature for 36h then washed with methanol 5 times and methylene chloride 5 times to give resin-bound amine **65**. The amine was coupled with an N-Fmoc amino acid (**66**) by treatment with HATU and i-Pr_2NEt in methylene chloride at room temperature for 48 h to provide resin **67**. Fmoc on resin **67** was removed by treatment with 30% piperidine in DMF and the resulting resin-bound amine was then reacted with fluoropyrimidine **68,** i-Pr_2NEt in DMSO:nBuOH (1:1) at 100 °C for 18 h and then washed with methanol, CH_2Cl_2 to give resin bound product **69**. The final product was cleaved off resin by treatment with TFA for 3 h to give product **70**.

The fluoropyrimidine **68** was prepared by stirring together 315 mg 6-imidazolyl-2,4-difluoropyrimidine (1.7 mmole), 265 mg of 3-chlorobenzylamine and 0.5 mL of i-Pr_2NEt in 30 mL of THF at 50 ^{0}C for 16 h, then cooling to room temperature. The reaction was diluted with ethyl acetate and washed with saturated NH_4Cl, H_2O, brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (eluted with 4:5:1 EtOAc : hexanes : MeOH) to give 160mg of **68** (more polar product as compared the other regioisomer).

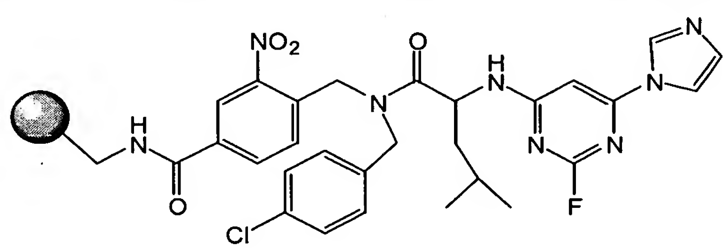
Scheme 2



NO2
Boc
HO
3 eq.
2
1 eq.
Lys—NH2
1
4 eq. DIC, 0.2 eq. DMAP
CH2Cl2, r.t., 20 h
3
1) 50%TFA-CH2Cl2
r.t., 2.5 h
2) 4 eq.HATU, 9 eq. i-Pr2NEt
CH2Cl2, r.t., 16 h
4 eq. N-Fmoc-D-Leu
NHFmoc
4
1) 30% Piperidine-DMF, r.t., 2 h
2) i-Pr2NEt, DMF,25 °C
5
i-Pr2NEt, DMF ,60 °C
H2N
6
Photolysis, MeOH-TFA
6a

Scheme 2 depicts a similar synthesis to that of Scheme 1, except the linker is photolytically cleavable instead of acid cleavable. As shown in Scheme 2, 2.5 g of amino functionalized TENTAGEL™ resin **1** (0.70 mmole) was suspended in 10 mL of CH_2Cl_2 and treated with 0.882 g of linker acid **2** (2.1 mmole), 0.44 mL of DIC (2.8 mmole), and 17 mg of DMAP (0.14 mmole). The mixture was shaken at room temperature for 17 h and then washed with CH_2Cl_2 ten times to give resin **3**.

1.13 g of resin **3** was treated with 50% TFA-CH_2Cl_2 at room temperature for 1.5 h and then washed with CH_2Cl_2 ten times, 15% Et_3N-CH_2Cl_2 for 10 min, and CH_2Cl_2 for 5 times. The deprotected resin was then suspended in 12 mL of CH_2Cl_2 and treated with 449 mg of N-Fmoc-D-Leu (1.27 mmole), 483 mg of HATU (1.27 mmole), and 0.50 mL of i-Pr_2NEt (2.85 mmole). The mixture was shaken for 19 h at ambient temperature and then washed 5 times to give resin **4**. Fmoc on resin **4** was removed by treatment with 30% piperidine in DMF and the resulting resin-bound amine (0.32 mmole) was then reacted with 182 mg of 6-imidazolyl-2,4-difluoropyrimidine (0.64 mmole), 0.34 mL of i-Pr_2NEt (1.92 mmole) in 10 mL of DMF at 23°C for 17 h and then washed with DMF, CH_2Cl_2 to give resin **5**. This reaction also produces the other regioisomer **5a**,

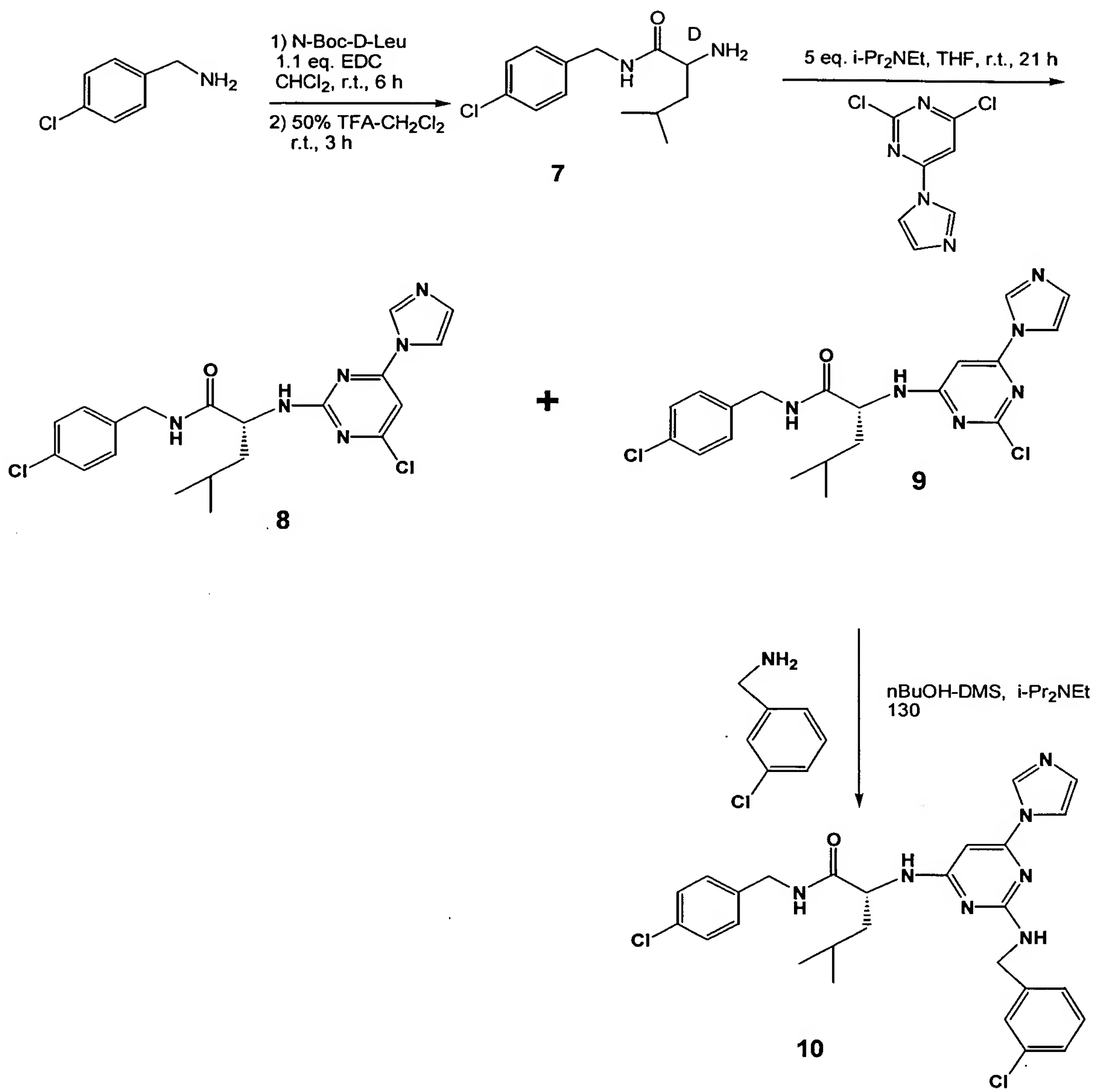


5a

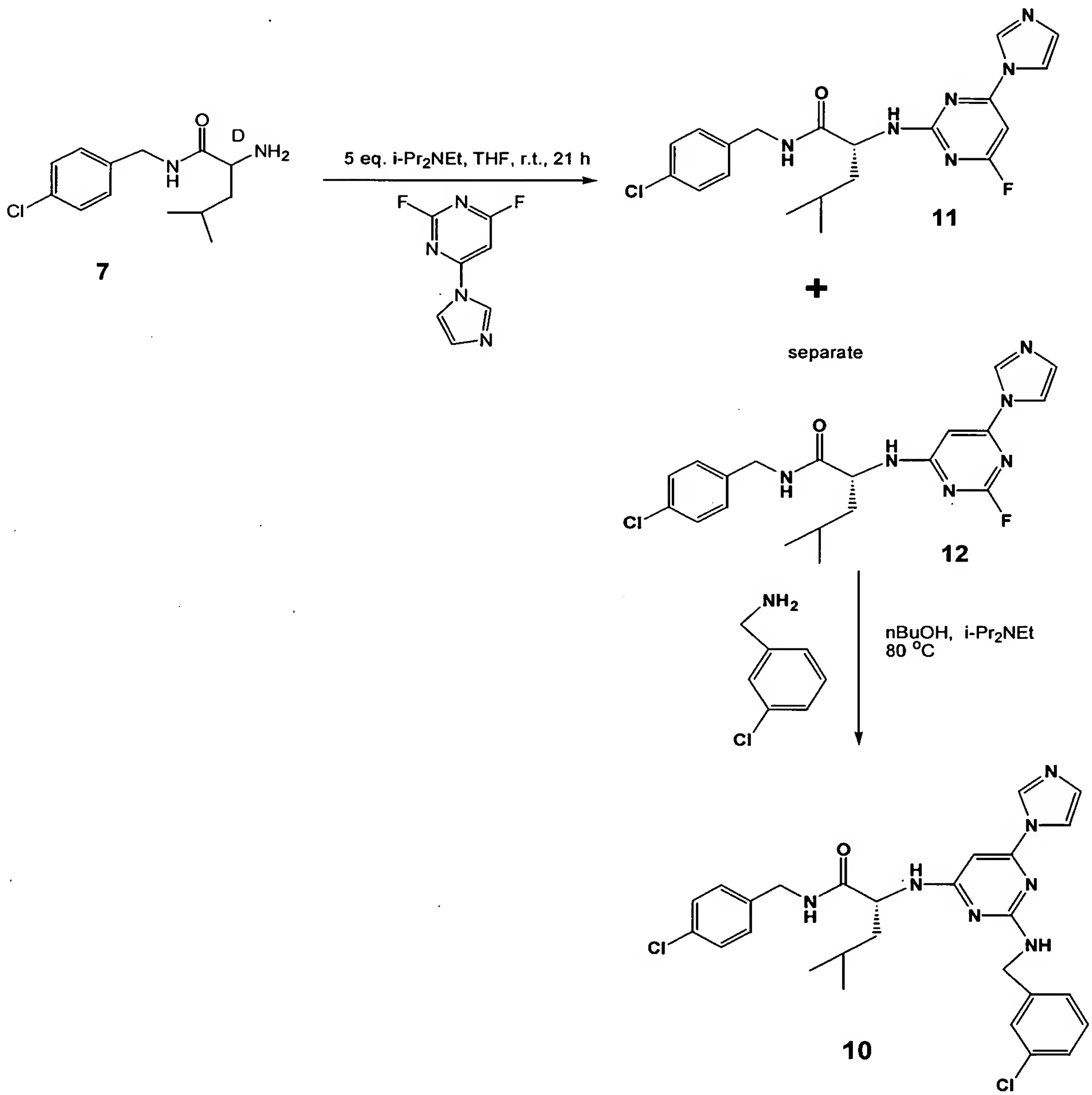
which provides entry into the series of pyrimidines of general formula IIa above. The two are separated after cleavage. For simplicity, only the further transformations in the IIb series are shown in Scheme 2. The resin-bound fluoride **5** was treated with 0.25 mL of 3,4-dichlorobenzylamine (1.6 mmole) in 15 mL of DMF and 0.30 mL of Hünig's base at 60 °C for 18h and then cooled to room temperature and washed with DMF, CH_2Cl_2. The final product was cleaved off

resin by photolysis in MeOH for 17 h to give 49.2 mg of crude product. Purification by flash chromatography (eluted with 5:5:1 EtOAc : hexanes : MeOH) gave 27.2 mg of **6a** (later determined to be mixture of two regioisomers with 1:1 ratio).

Scheme 3


1) N-Boc-D-Leu
1.1 eq. EDC
CHCl2, r.t., 6 h
2) 50% TFA-CH2Cl2
r.t., 3 h
7
5 eq. i-Pr2NEt, THF, r.t., 21 h
8
9
nBuOH-DMS, i-Pr2NEt
130
10

Scheme 4

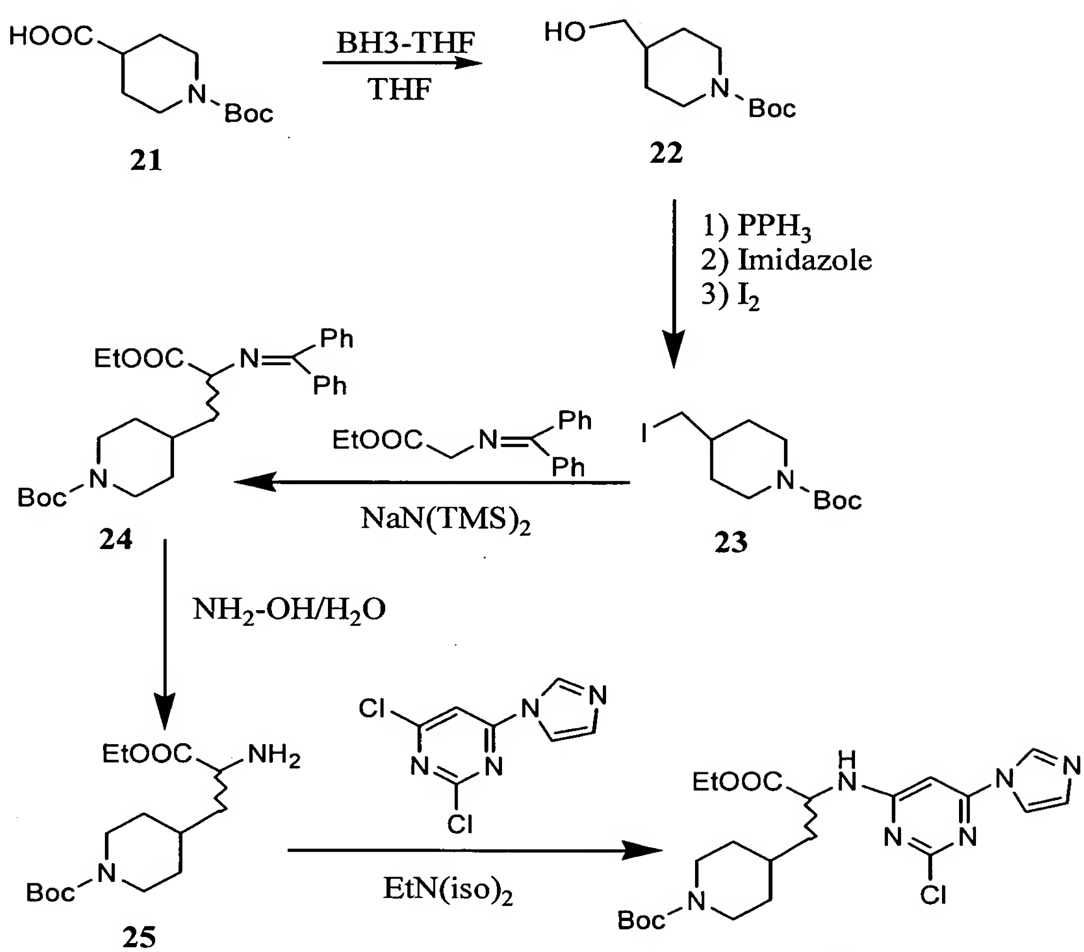

D
NH2
Cl
7
5 eq. i-Pr2NEt, THF, r.t., 21 h
F
N
F
N
N
N
O
H
N
N
N
N
F
11
separate
12
NH2
Cl
nBuOH, i-Pr2NEt
80 °C
NH
10

Scheme 3 illustrates a solution phase synthesis via chloropyrimidines and Scheme 4 illustrates a solution phase synthesis via fluoropyrimidines. As shown in Scheme 3, EDC (5.18 g, 26.47 mmole) was added into a solution of N-Boc-D-leucine (6.0 g, 24.07 mmole) in 250 mL of CH_2Cl_2, followed by 2.99 mL of 4-chlorobenzylamine (24.07 mmol). The mixture was stirred at room temperature for 4 h then diluted with ethyl acetate and washed with 1 N HCl twice, saturated $NaHCO_3$ and brine twice, dried over $MgSO_4$ and concentrated to give 7.92 g of crude amide product which was treated with 50% TFA in CH_2Cl_2 at room temperature for 4 h. The solvent was removed and the residue was taken up into ethyl acetate and washed with 2 N NaOH aqueous solution, then brine, dried over $MgSO_4$ and concentrated to give amine product **7** quantitatively.
Three hundred ninety milligrams of the free amine **7** (1.1 mmole) was treated with 0.6 mL of i-Pr2NEt and 500 mg 6-imidazolyl-2,4-dichloropyrimidine (2.0 mmole) in DMF at 50 ^{0}C for 16 hr, then diluted with ethyl acetate and washed with saturated NH_4Cl, H_2O, brine, dried over $MgSO_4$ and concentrated and purification by flash chromatography (eluted with 8:10:1 EtOAc : Hexanes : MeOH) to give 200 mg of **8** and 130 mg of **9** Ninety two milligrams of **9** (0.21 mmole) in 3 mL of n-butanol was treated with 0.9 mL of 3-chlorobenzylamine and 1 mL of i-Pr_2NEt at 100 ^{0}C for 16 h, then cooled to room temperature, diluted with ethyl acetate and washed with saturated NH_4Cl, H_2O, brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (eluted with 4:5:1 EtOAc : Hexanes : MeOH) o give 97.2 mg of **10**.

Alternatively, as illustrated in Scheme 4, 280 mg of the free amine **7** (1.1 mmole) was treated with 0.25 mL of i-Pr_2NEt and 200 mg of 6-imidazolyl-2,4-difluoropyrimidine (1.1 mmole) in THF at room temperature for 13 hr, then diluted with ethyl acetate and washed with saturated NH_4Cl, H_2O, brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (eluted with 8:10:1 EtOAc : hexanes : MeOH) to give 35 mg of **11** (less polar product) and 80 mg of **12** (more polar product). Four hundred fifty milligrams of **12** (1.08

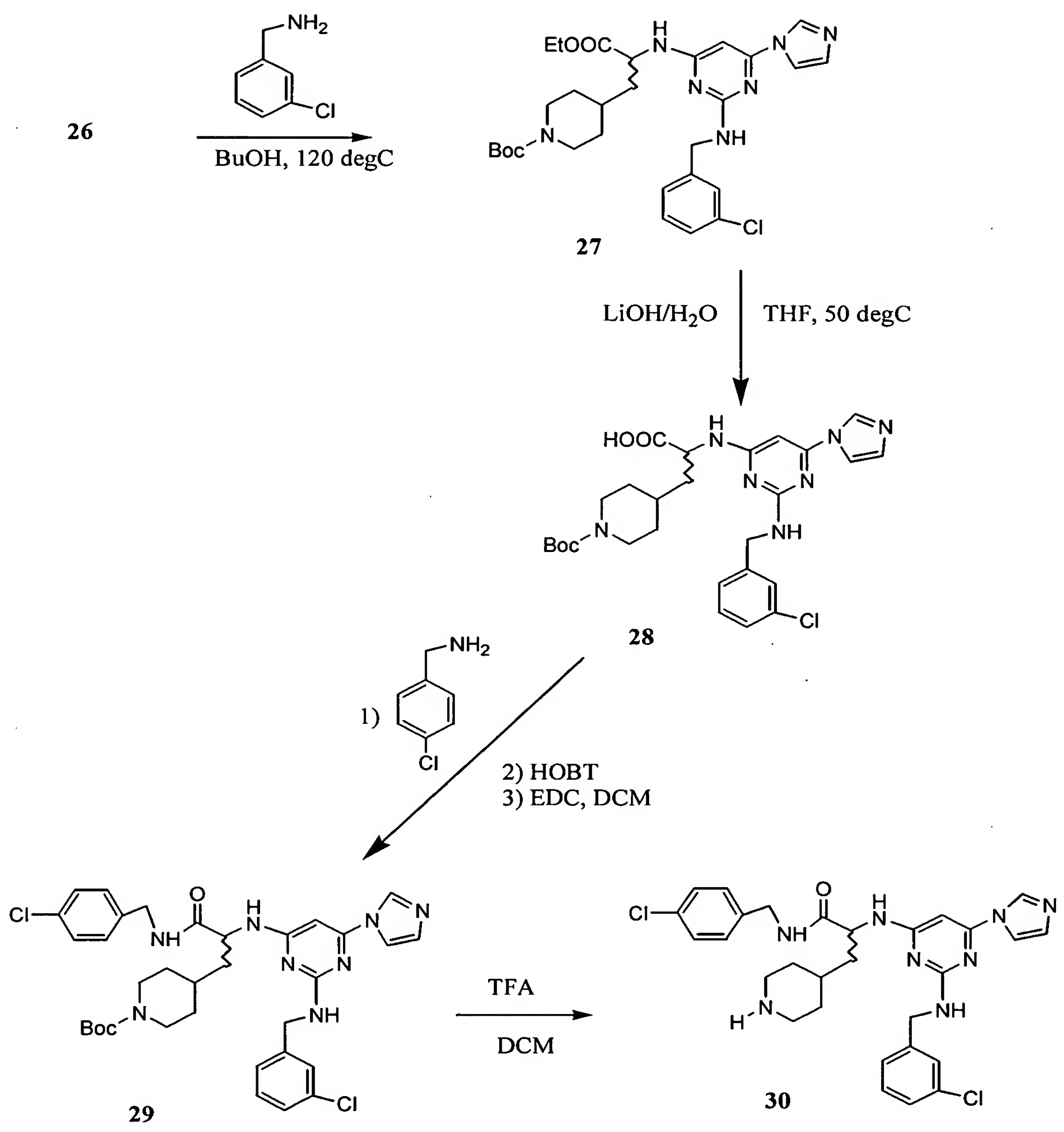
mmole) in 50 mL of THF or n-butanol was treated with 1.7 g of 3-chlorobenzylamine and 5 mL of i-Pr_2NEt at 80 ^0C for 16 h then diluted with ethyl acetate and washed with saturated NH_4Cl, H_2O, brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (eluted with 6:12:1 EtOAc : hexanes : MeOH) to give 350 mg of **10**.

Scheme 5



21 22 23 24 25 26

Scheme 5 (continued)



Scheme 5 illustrates a synthesis of a member of the subgenus in which R^1 is heterocycloalkyl. According to Scheme 5 a dry 500 mL round bottom flask (oven-heated/argon cooled), was charged with 25 g (109.2 mmol) of Boc-isonipecotic acid (**21**). The flask was purged with argon, and 150 mL of dry THF were injected by syringe into the air-free system. The mixture was then stirred while being cooled to 0°C, and an oil-bubbler was attached, then 131 mL of a 1 M solution of borane/THF (131 mmol) were injected into the solution slowly, and the solution was stirred for ½ hour. Methanol was dripped into the solution slowly until bubbles ceased to be evolved. The solution was washed with 200 mL of a saturated sodium bicarbonate solution, and extracted twice with ethyl acetate, and the organic layer was dried over magnesium sulfate. The yield of the reaction was 22.44g (96%) of the **22** product as a white solid. ^{1}H NMR in $CDCl_3$: a 3H multiplet from 0.85-1.2 ppm, a 9H singlet at 1.45 ppm, a 4H multiplet 1.455-1.8 ppm, a 2H broad signal at 2.65 ppm, a 1H broad signal at 3.45 ppm, and a 1H broad signal at 3.6 ppm.

A 250 mL round bottom flask was charged with 5.8 g (27 mmol) of **22**, 8.5 g (32.37 mmol) of triphenylphosphine, and 2.2 g (32.37 mmol) of imidazole. One hundred millileters of methylene chloride were added, and the resulting solution was stirred at 0°C for about 5 minutes. Finally, 8.2 g (32.37 mmol) of iodine were added and the solution was stirred at 0°C for 5 minutes and at room temp for about 1 hour. The reaction mixture was diluted with 200 mL of hexane, and the triphenylphosphine oxide precipitate was filtered off (this was repeated until all precipitate was removed). The crude mixture was purified by flash chromatography using a 5%-10% ethyl acetate/hexane solvent system. A Phosphomolybdic acid stain (PMA), was used to see the product on the TLC plate. The resulting yield of pure **23** as an oil was 2.6g (30%). ^{1}H NMR in $CDCl_3$: 2H quartet at 1.1 ppm (J=12 Hz), a 9H singlet at 1.4 ppm, a 1H broad signal at 1.55 ppm, a 2H doublet at 1.75(J=12 Hz), a 2H broad signal at 2.65 ppm, a 2H doublet at 3.05 ppm (J=6 Hz),

and a 2H broad signal at 4.1 ppm. The R_f=0.13 using a 5% ethyl acetate/hexane solvent system.

A dry 250 mL round bottom flask (oven heated/argon cooled), was charged with 1.3 g (5.13mmol) of N-(diphenylmethylene) glycine ethyl ester. The flask was purged with argon, and 100 mL of dry THF were injected into the air-free system. The resulting solution was cooled to -78C with stirring, and 6.2 mL (6.15mmol) of a 0.1 M solution of sodium hexamethyldisilazane in THF were injected into the solution. The reaction was stirred at -78°C for ½ hr, and a solution of 2 g of **23** in dry THF was injected into the system. The solution was stirred at -78°C for 1 hr, at 0°C for 1 hr, and at room temp overnight. The reaction mixture was washed with a solution of 1 g (6.15 mmol) of citric acid in water, and diluted with 200 mL of ethyl acetate. The organic layer was extracted and dried over magnesium sulfate. The crude mixture was purified by flash chromatography using a 10% ethyl acetate/hexane solvent system. The yield was 1.45 g (61%) of solid product **24**. ^{1}H NMR in $CDCl_3$: A 3H broad multiplet from 0.8-1.15 ppm, a 4H broad signal at 1.25 ppm, a 9H singlet at 1.4 ppm, a 2H broad signal at 1.5 ppm, a 1H broad triplet at 1.85 ppm, a 2H broad quartet at 2.6 ppm, a 2H broad signal at 3.95 ppm, a 2H broad signal at 4.15 ppm, a 2H triplet at 7.15 ppm (J=3.6 Hz), a 6H multiplet from 7.25-7.5 ppm, and a 2H doublet at 7.6 ppm (J=9 Hz). The R_f=0.22 suing a 10% ethyl acetate/hexane solvent system. ESI MS at 465 MH+.

A 100 mL round bottom flask was charged with 0.35 g (0.75 mmol) of **24**, and 20 mL of ethanol were added to the flask. With stirring, 0.5 mL of a 50% (by weight) solution of hydroxylamine was added followed by 0.5 mL of glacial acetic acid (5 minutes later). The reaction was stirred for 10 minutes, until the starting material disappeared by TLC. The reaction mixture was diluted with 100 mL ethyl acetate, 20 mL of a brine solution was added, followed by basification using 0.5 M NaOH. The organic layer was extracted, and the aqueous layer was then extracted with two 20 mL portions of methylene chloride. The combined organic layers were

dried over magnesium sulfate. The crude mixture was purified by flash chromatography using a 55% ethyl acetate/hexane solvent system. A ninhydrin stain was used to see the product spot on the TLC plate. The yield of pure **25** as an oil was 0.25 g (96%). ^{1}H NMR in $CDCl_3$: A 1H multiplet from 0.9-1.05 ppm, a 3H broad triplet at 1.1 ppm, a 3H triplet at 1.25 ppm (J=6 Hz), an 11H broad signal at 1.4 ppm, a 3H multiplet from 1.5-1.8 ppm, a 2H broad triplet at 2.7 ppm, a 3H quartet at 3.45 ppm (J=3.6 Hz), and a 4H multiplet from 4-4.2 ppm. The R_f= 0.22 using a 55% ethyl acetate/hexane solvent system.

A 50 mL round bottom flask was charged with 0.310 g (1 mmol) of **25** and 5 mL of DMF. With stirring, 0.22 g (1 mmol) of the pyrimidine/imidazole subunit, and 0.35 mL (2 mmol) of diisopropylethylamine (Hünig's base) were added. The mixture was stirred at 90°C overnight. The reaction mixture was diluted with 200 mL of ethyl acetate, and washed with water. The organic layer was extracted and dried over magnesium sulfate. The crude mixture was purified by flash chromatography using an 80%-90% ethyl acetate/hexane solvent system. The yield of the reaction was 0.14 g of the regio-isomer with substitution of the pyrimidine at the 2-position and 0.12 g (25%) of the desired regio-isomer **36** (oil), (total yield is 54%). ^{1}H NMR in $CDCl_3$: a 1H multiplet from 0.9-1.05 ppm, a 3H broad triplet at 1.15 ppm, a 2H triplet at 1.3 ppm (J=6Hz), a 9H singlet at 1.45 ppm, a 2H broad signal at 1.7 ppm, a 2H broad signal at 1.85 ppm, a 2H broad triplet at 2.65 ppm, a 2H broad signal at 4.1 ppm, a 2H quartet at 4.2 ppm (J=2.4 Hz), a 1H broad signal at 4.9 ppm, a 1H doublet at 6.05 ppm (J=9 Hz), a 1H broad singlet at 6.3 ppm, a 1H singlet at 7.15 ppm, a 1H singlet at 7.5 ppm, and a 1H singlet at 8.3 ppm. The R_f of the desired regio-isomer was about 0.22 using an 80% ethyl acetate/hexane solvent system. The pure product gave a molecular ion of 480, MH+.

A 50 mL round bottom flask was charged with 0.12 g (0.25 mmol) of **26**, 0.142 g (1mmol) of 3-chlorobenzylamine, and 5 mL of dry n-butanol. The solution was stirred at 120°C overnight. The reaction mixture was diluted with 200 mL of

ethyl acetate, and washed with water. The organic layer was extracted and dried over magnesium sulfate. The crude mixture was purified by flash chromatography using a 90%-95% ethyl acetate/hexane solvent system. The yield was 0.125 g (87%) of **27** as an oil. ^{1}H NMR in $CDCl_3$: a 1H triplet at 0.9 ppm (J=6), a 2H broad signal at 1.1 ppm, a 3H triplet at 1.25 ppm (J=4.8 Hz), a 9H singlet at 1.45 ppm, a 5H broad signal at 1.65 ppm, a 2H broad signal at 2.6 ppm, a 4H broad signal at 4.1 ppm, a 2H doublet at 4.55 ppm (J=6 Hz), a 1H broad signal at 4.7 ppm, a 1H doublet at 5.4 ppm (J=9 Hz), a 1H singlet at 5.75 ppm, a 1H singlet at 7.1 ppm, a 3H singlet at 7.2 ppm, a 1H singlet at 7.35 ppm, a 1H singlet at 7.5 ppm, and a 1H singlet at 8.25 ppm. The R_f of the product was about 0.28 using an 80% ethyl acetate/hexane solvent system. The pure product gave a molecular ion of 584, MH+.

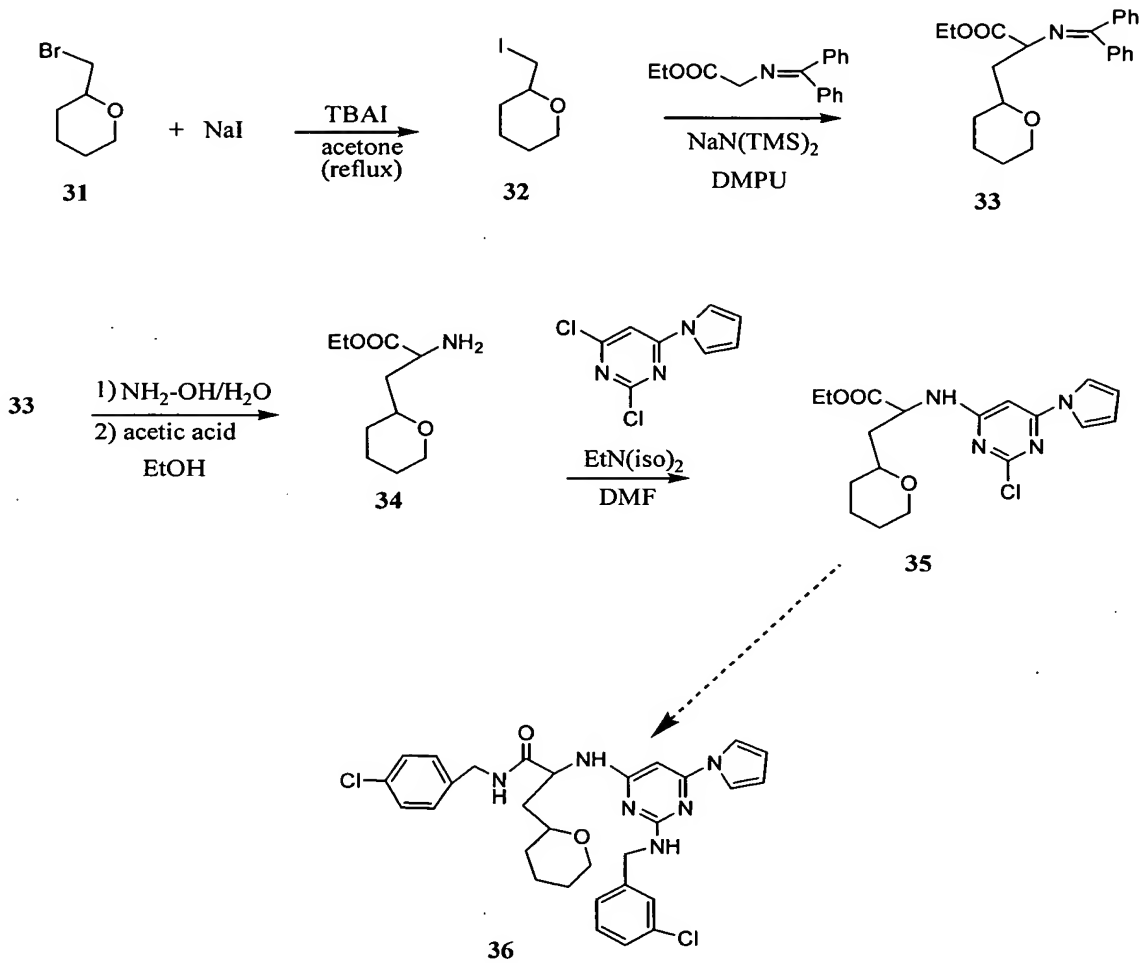
A 50 mL round bottom flask was charged with 0.125 g (0.214 mmol) of **27** and 10 mL of THF. With stirring, a solution of 0.09 g (2.14 mmol) of lithium hydroxide in 10 mL of water was added. The solution was heated at 55°C for 2 hr. The reaction mixture was diluted with 200 mL of ethyl acetate, and washed with a solution of 0.412 g (2.14 mmol) of citric acid in water to neutralize the excess base present. The organic layer was extracted and dried over magnesium sulfate. The crude mixture was purified by flash chromatography using an 95% ethyl acetate/methanol solvent system. The yield was 0.1 g (83%) of pure **28** as a white solid. ^{1}H NMR in $CDCl_3$: a 1H broad signal at 0.9 ppm, a 3H broad signal at 1.1 ppm, a 2H triplet at 1.25 ppm (J=6 Hz), a 9H singlet at 1.4 ppm, a 4H broad signal at 1.65 ppm, a 2H broad signal at 2.45 ppm, a 3H broad signal at 4 ppm, a 2H broad signal at 4.3-4.8 ppm, a 1H broad signal at 5.85 ppm, a 1H singlet at 7.05 ppm, a 3H singlet at 7.15 ppm, a 1H doublet at 7.25 ppm (J=3.6), a 1H singlet at 7.5 ppm, and a 1H singlet at 8.5 ppm. The R_f of the product was about 0.08 using a 95% ethyl acetate/methanol solvent system. The pure product gave a molecular ion of 556, consistent with its molecular weight of 555,MH+.

A 50 mL round bottom flask was charged with 0.099 g (0.178 mmol) of **28** and 20 mL of methylene chloride. With stirring, 0.048g (0.356 mmol) of 1-hydroxybenzotriazole (HOBT) and 0.068 g (0.356 mmol) of 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDC), were added to the solution, then 1 mL of DMF was added to aid in solubility, and the solution was stirred for 20 minutes, until the acid intermediate spot disappeared by TLC. Fifty milligrams (0.356 mmol) of 4-chlorobenzylamine was added to the solution and it was stirred for 2 hrs. The reaction mixture was diluted with 200 mL of ethyl acetate and washed successively with solutions of 0.5 M HCl, 0.5 M NaOH, and brine. The organic layer was extracted and dried over magnesium sulfate. The crude mixture was purified by flash chromatography using 100%-98% ethyl acetate/methanol as the solvent system. The yield was 0.085 g (71%) of pure **29** as an oil. ^{1}H NMR in $CDCl_3$: a 4H multiplet from 0.9-1.3 ppm, a 9H singlet at 1.4 ppm, a 5H broad signal at 1.6 ppm, a 1H multiplet from 1.75-2.15 ppm, a 2H broad signal at 2.6 ppm, a 2H singlet at 3.85 ppm, a 1H broad signal at 4.05 ppm, a 4H multiplet from 4.3-4.6 ppm, a 1H doublet at 5.3 ppm (J=6), a 1H singlet at 5.7 ppm, a 2H singlet at 7.1 ppm, a 7H multiplet from 7.15-7.3 ppm, a 1H singlet at 7.45 ppm, and a 1H singlet at 8.25 ppm. The R_f of the product was about 0.24 using a 95% ethyl acetate/methanol solvent system. The pure product gave a molecular ion of 679, consistent with its molecular weight of 678 amu.

A 50 mL round bottom flask was charged with 0.020 g (0.03 mmol) of **29** and 3 mL of methylene chloride. With stirring, 1.5 mL (0.02 mmol) of trifluoroacetic acid was added, and the solution was stirred for about 20 minutes, until the Boc-containing intermediate disappeared by TLC. The reaction mixture was diluted with 10 mL toluene and evaporated twice. The product **30** was diluted with 50 mL ethyl acetate, and washed with 0.5 M NaOH. ^{1}H NMR in $CDCl_3$: a 5H multiplet from 0.75-1 ppm, a 5H multiplet from 1.5-1.8 ppm, a 1H singlet at 1.95 ppm, a 2H quartet at 2.6 ppm (J=14), a 1H broad signal at 3.1 ppm, a 2H singlet at 3.65 ppm, a 4H multiplet from 4.-4.7 ppm. A 1H singlet at 5.9 ppm, a 9H

multiplet from 7.05-7.15 ppm, a 1H singlet at 7.5 ppm and a 1H singlet at 8.3 ppm. The pure product gave a molecular ion of 579, consistent with its molecular weight of 578 amu.

Scheme 6



As outlined in Scheme 6, a 500 mL round bottom flask was charged with 10 g (55.84 mmol) of **31**, 84 g (558.4 mmol) of sodium iodide, 20.63 g (55.84 mmol) of t-butyl ammonium iodide, and 250 mL acetone. The mixture was stirred at reflux overnight. The reaction mixture was filtered to eliminate excess sodium iodide, and was diluted with 100 mL hexane. The mixture was filtered again to remove more of the remaining sodium iodide. This was repeated until no precipitate formed when the mixture was diluted with hexane. The reaction yield was 9.66 g (77%) of pure 2-(iodomethyl)tetrahydro-2H-pyran **32** as an oil. ^{1}H NMR in $CDCl_3$ was consistent with structure. R_f=0.55, using a 2% ethyl

acetate/hexane solvent system and a phosphomolybdic acid stain. The product did not give a mass spec signal.

A dry 100 mL round bottom flask (oven heated/argon cooled) was charged with 3.2 g (11.80 mmol) of N-(diphenylmethylene) glycine ethyl ester and purged with argon. Thirty-five milliliters of dry DMPU and 15 mL of dry THF were injected by syringe into the air-free system. The resulting solution was cooled to -78°C, and 17.70 mL (1.5 mmol) of a 0.1 M solution of sodium hexamethylsilazane in THF was injected into the system, which was then stirred at -78°C for 20 minutes. Finally, an air-free solution of 4 g (17.70 mmol) of **32** in dry THF was injected into the system, which was then stirred at -78°C for ½ hr, 0°C for ½ hr, and room temp overnight. The reaction mixture was diluted with 300 mL of ethyl acetate and washed 5 times with 50 mL portions of water to remove the DMPU. The organic layer was extracted and dried over magnesium sulfate. The crude mixture was purified by flash chromatography 4-11% ethyl acetate/hexane solvent system. The yield of the reaction was 1.57 g of the less polar diastereomer of **33**, and 0.33 g of the more polar diastereomer of **33**. The overall yield was 1.9 g (44%). ^{1}H NMR in $CDCl_3$ was consistent with structures. The diastereomers have partial overlap by TLC, R_f=0.55 using a 5% ethyl acetate/hexane solvent system. The product gave a molecular ion of 366, consistent with its molecular weight of 365.

Note: Throughout the rest of the synthesis, the procedures involve the use of the more polar diastereomer, for the sake of clarity.

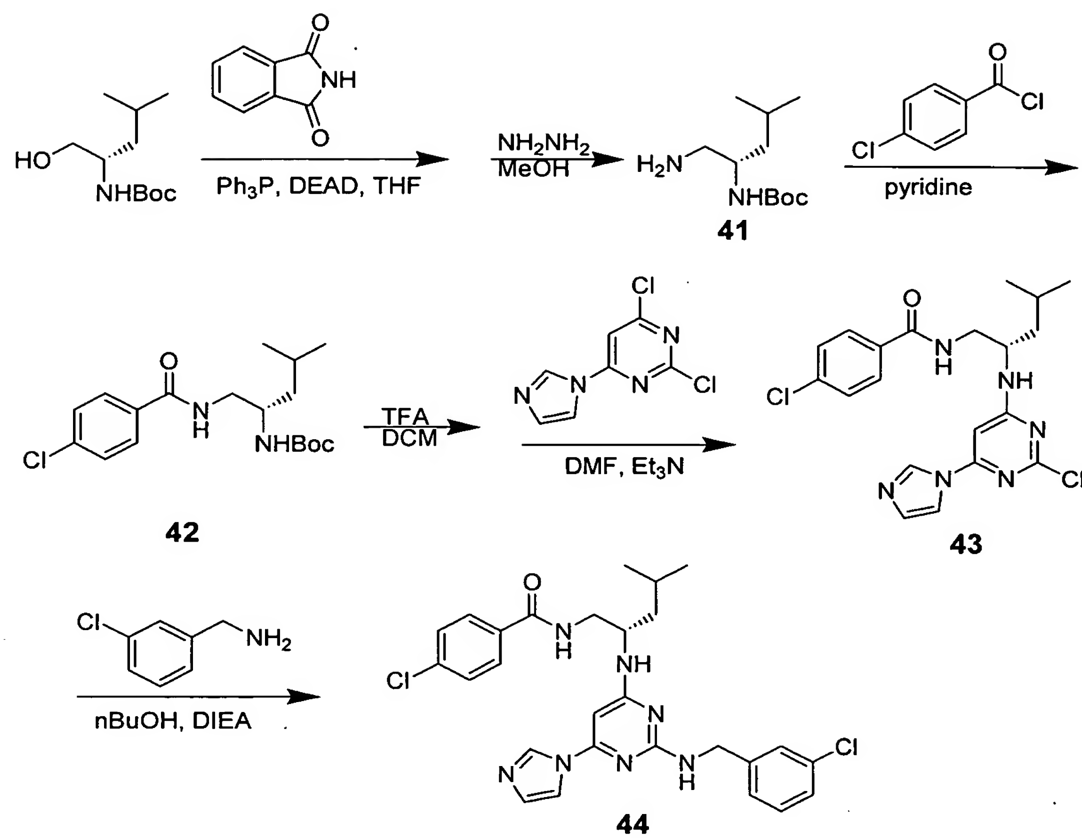
The deprotection and work-up of **33** to give **34** follows the same procedure as that for the isonipecotic analogue (see the synthesis of **25** in that sequence).

The crude mixture was purified by flash chromatography using an 80-90% ethyl acetate/hexane solvent system and a ninhydrin stain. The yield for the reaction was 68%. ^{1}H NMR in $CDCl_3$ was consistent with structures. The R_f=0.15 using a 90% ethyl acetate/hexane solvent system. The product gave MH+ @ 202.

The coupling and work-up of **34** with the dichloropyrimidine-pyrrole intermediate follows the same procedure as that for the isonipecotic analogue with the dichloropyrimidine-imidazole intermediate (see the synthesis of **26** in that sequence). The crude mixture was purified by flash chromatography using a 10-20% ethyl acetate/hexane solvent system. The yield for the reaction was 25% for the desired more polar regio-isomer, and 62% for the total yield for both regio-isomers. ^1H NMR in $CDCl_3$ was consistent with structure. The R_f=0.15 using a 10% ethyl acetate/hexane solvent system. The product gave MH+ @ 379.

The remaining steps from **35** to **36** follow the corresponding procedures as for the isonipecotic analogue (see Scheme 5). The crude **36** was purified by flash chromatography using a 16-25% ethyl acetate/hexane solvent system. ^1H NMR in $CDCl_3$ was consistent with structure. The R_f=0.55 using a 20% ethyl acetate/hexane solvent system. The product gave MH+ at 615.

Scheme 7



Scheme 7 depicts an exemplary synthesis wherein m > zero and A=A[2]. To Boc-D-leucinol (2.7g, 12.4 mmol), triphenylphosphine (3.25g, 12.4 mmol), and phthalimide (1.82g, 12.4 mmol) in 25 mL of dry THF was added DEAD dropwise. The solution was stirred at room temperature overnight, concentrated and taken up in MeOH. To this solution was added hydrazine (780 mL, 24.8 mmol) and heated to reflux for 2 hours. The mixture was allowed to cool to room temperature, and the white precipitate filtered. The mother liquor was concentrated, taken up in EtOAc and washed with 1N HCl. The aqueous layer was then cooled in an ice bath, basified with 3N NaOH, and extracted with EtOAc. The organic layer was dried over K_2CO_3 and concentrated to yield **41** as a clear oil. (0.75g, 3.5 mmol, 28%).

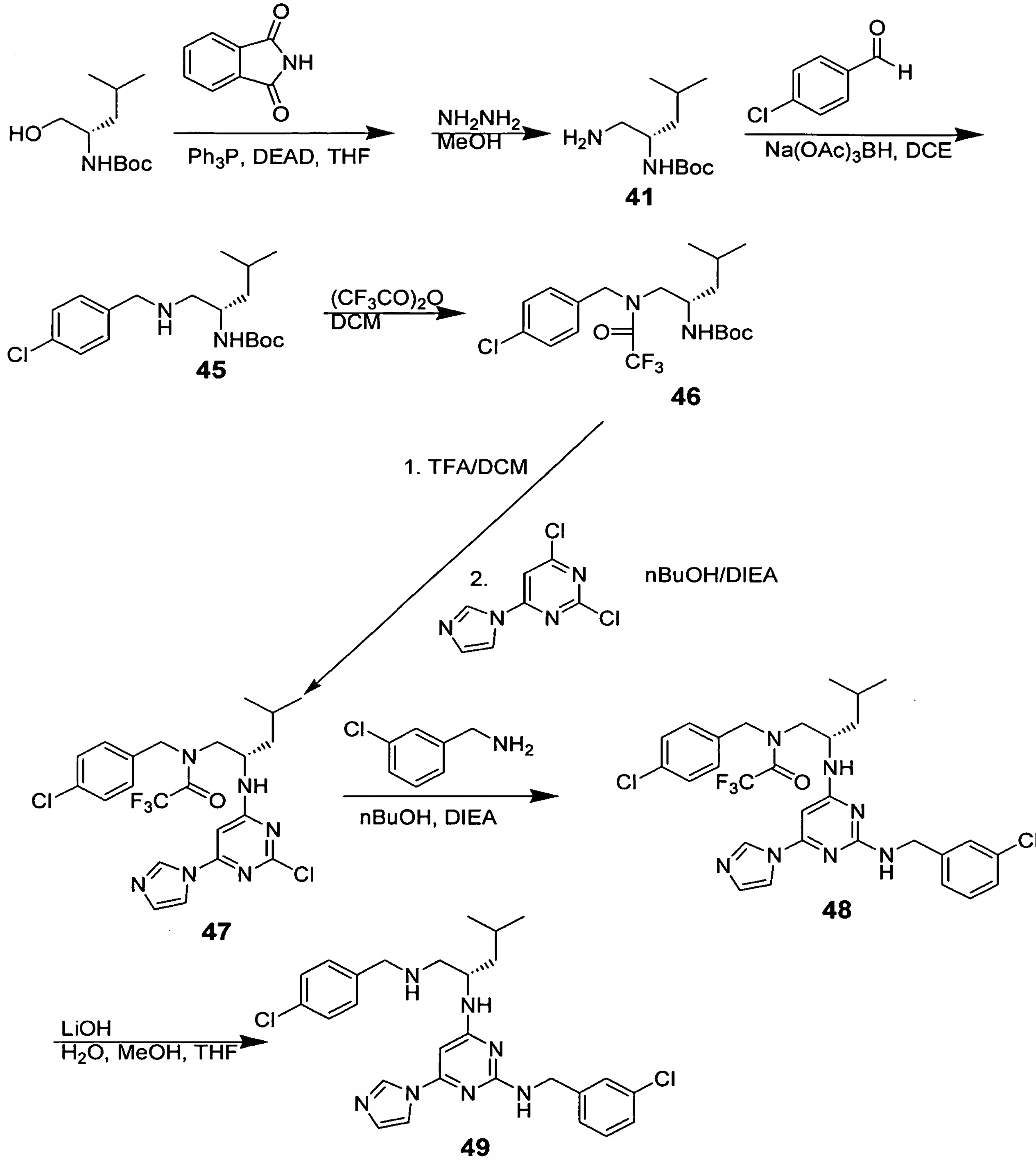
To **41**(0.3g, 1.4 mmol) in 15 mL pyridine was added 4-chlorobenzoyl chloride (194

mL, 1.5 mmol) and the mixture was stirred at room temperature for 4 hours. The reaction was poured into 200 mL water and the precipitate filtered. The resulting solid was taken up in DCM and washed with saturated $NaHCO_3$ and 1M $KHSO_4$. The organic layer was dried over $MgSO_4$ and concentrated to yield **42** as a pale white solid. (0.30g, 0.84 mmol, 61%)

One hundred sixty-five milligrams of **42** (0.46 mmol) was taken up in 10 mL of DCM and 5 mL TFA was added. After 30 minutes the solution was concentrated, taken up in DMF and basified with excess triethylamine. To this was added 2,4-dichloro-6-imidazolylpyrimidine (100 mg, 0.46 mmol) and the mixture stirred at room temperature overnight. The reaction mixture was concentrated and the resulting oil purified on a silica gel column, eluting with 2%MeOH/DCM to yield **43**. (42 mg, 0.1 mmol, 21%).

To **43** (30 mg, 0.07mmol) in 10 mL n-butanol was added DIEA (60 mL, 0.35 mmol) and 3-chlorobenzylamine (200 mL, 1.4 mmol), and the reaction was heated to 100°C overnight. The solution was concentrated and the resulting oil purified on a silica gel column, eluting with 5% MeOH/DCM to yield **44** as a foam. (31 mg 0.06 mmol, 82%).

Scheme 8



HO
NHBoc
NH
Ph$_3$P, DEAD, THF
NH$_2$NH$_2$
MeOH
H$_2$N
NHBoc
41
Cl
H
Na(OAc)$_3$BH, DCE
N
H
NHBoc
45
(CF$_3$CO)$_2$O
DCM
CF$_3$
46
1. TFA/DCM
2.
nBuOH/DIEA
F$_3$C
NH
47
NH$_2$
nBuOH, DIEA
48
LiOH
H$_2$O, MeOH, THF
49

Scheme 8 illustrates a similar synthesis to that of Scheme 7 in which A is R^4NH-.

Two hundred seventy milligrams of **41** (1.25 mmol), 4-chlorobenzaldehyde (193 mg, 1.4 mmol) and sodium triacetoxyborohydride (0.4 g, 1.9 mmol) were combined in 20 mL dichloroethane and stirred at room temperature overnight. The mixture was then concentrated, taken up in DCM and washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated to yield **45** which was used without further purification. (0.40g, 1.2 mmol, 94%).

To **45** (0.35 g, 1.03 mmol) in DCM cooled in an ice bath was added trifluoroacetic anhydride (145 μl, 1.03 mmol) slowly. After 10 minutes the solution was concentrated, taken up in DCM and washed with 1M $KHSO_4$. The organic layer was dried over $MgSO_4$ and concentrated to yield **46** which was used without further purification. (0.32 g, 0.75 mmol, 75%).

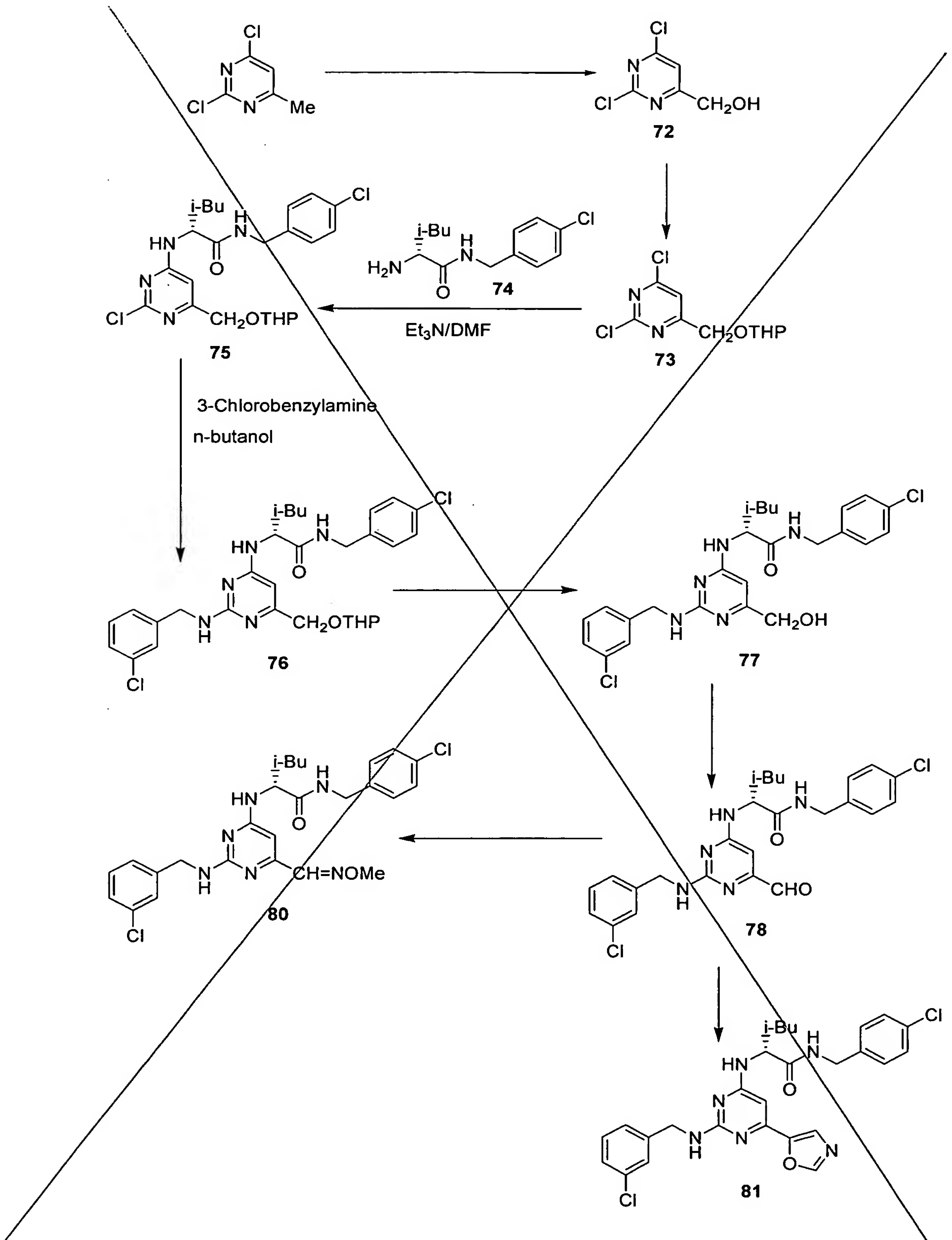
Three hundred twenty milligrams of **46** (0.73 mmol) was taken up in 10 mL of DCM and 5 mL TFA was added. After 30 minutes the solution was concentrated, taken up in DMF and basified with excess triethylamine. To this was added 2,4-dichloro-6-imidazolylpyrimidine (190 mg, 0.88 mmol) and stirred at room temperature overnight. The reaction mixture was concentrated and the resulting oil purified on a silica gel column, eluting with 2%MeOH/DCM to yield **47**. (100 mg, 0.19 mmol, 27%).

To **47** (100 mg, 0.19) in 5 mL of n-butanol was added DIEA (60 μl, 0.35 mmol) and 3-chlorobenzylamine (200 μL, 1.4 mmol) and heated to 100°C overnight. The solution was concentrated and the resulting oil purified on a silica gel column, eluting with 5% MeOH/DCM to yield **48** as a foam. (10 mg 0.02 mmol, 9%).

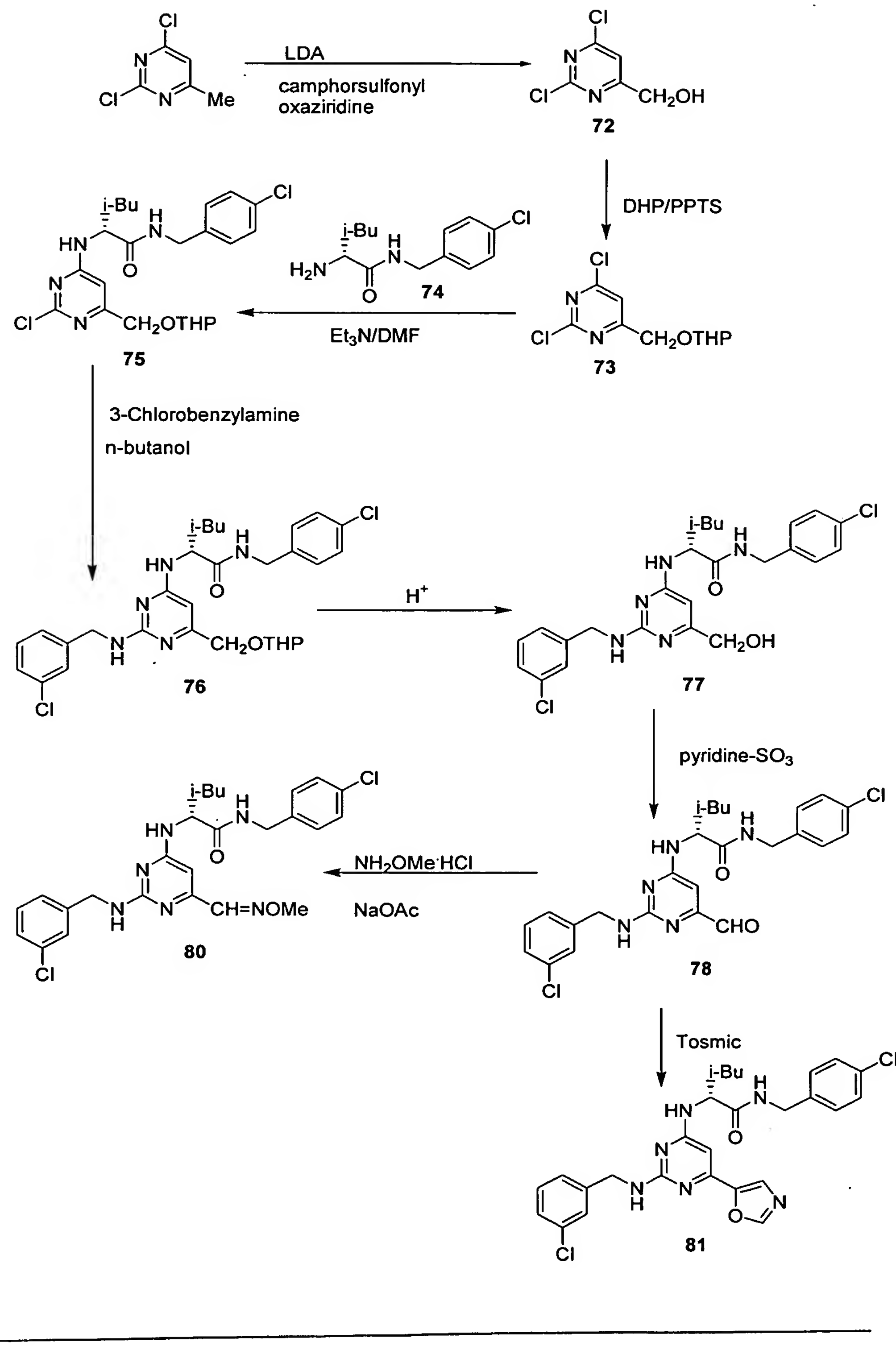
A solution of **48** (10 mg 0.02 mmol) in 10 mL of MeOH:H_2O:THF (1:1:1)

was refluxed for 6 hours with excess LiOH. The solution was concentrated, taken up in DCM and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated to yield **49**. (6 mg, 0.01 mmol, 50%)

Scheme 9


Cl
N
Cl
N
Me
Cl
N
Cl
N
CH2OH
72
i-Bu
H
HN
N
O
Cl
N
Cl
N
CH2OTHP
75
i-Bu
H2N
H
N
O
74
Cl
Et3N/DMF
Cl
N
Cl
N
CH2OTHP
73
3-Chlorobenzylamine
n-butanol
76
CH2OTHP
77
CH2OH
78
CHO
80
CH=NOMe
81

Scheme 9


LDA
camphorsulfonyl oxaziridine
Cl
N
Cl
N
Me
CH_2OH
72
DHP/PPTS
73
CH_2OTHP
i-Bu
H
H_2N
O
74
Et$_3$N/DMF
75
HN
3-Chlorobenzylamine
n-butanol
76
H$^+$
77
pyridine-SO$_3$
78
CHO
$NH_2OMe{\cdot}HCl$
NaOAc
CH=NOMe
80
Tosmic
81

According to Scheme 9, a solution of 2,4-dichloro-6-methylpyrimidine (710 mg, 4.36 mmol) in 4.5 mL of dry THF was added dropwise to a solution of freshly prepared LDA (466 mg, 4.36 mmol) in 17.5 mL of dry THF at -78 °C. After stirring for additional 15 min, the solution of the anion formed was cannulated into a solution of camphorsulfonyloxaziridine (1.0 g, 4.36 mmol) in 11 mL of dry THF maintained at -78 °C. The reaction mixture was stirred in dry ice-acetone bath for 1 h, then quenched with acetic acid and brought to room temperature. Aqueous work up and chromatography (silica gel, hexane:ethyl acetate, 4:1) gave 300mg of **72**.

A solution of 2,4-dichloro-6-hydroxymethylpyrimidine (1.8 g, 10.0 mmol), dihydropyran (1.26 g, 15 mmol) and PPTS (502 mg, 2.0 mmol) in 20 mL of dry chloroform was stirred for 1 h at RT. TLC indicated complete absence of the starting material. Aqueous work up and chromatography (silica gel, hexane:ethyl acetate, 85:15) gave 1.02 g of the THP ether **73**.

A solution of leucine amide **74** (254 mg, 1.0 mmol), THP ether (263 mg, 1 mmol) and Et_3N (101 mg, 1 mmol) in 10 mL of dry THF was refluxed for 24 h. Evaporation of the solvent, followed by aqueous work up and chromatography (silica gel, hexane:ethyl acetate, 65:35) gave 174 mg of the desired isomer **75**.

A solution of **75** (174 mg, 0.36 mmol) and 3-chlorobenzylamine (142 mg, 1.0 mmol) in 15 mL of *n*-butanol was refluxed overnight. The solvent was removed *in vacuo* and the residue was purified by chromatography (silica gel, ethyl acetate) to provide 52 mg of **6**.

A solution of **76** (52 mg, 0.085 mmol) and PPTS (50 mg, 0.2 mmol) in 12 mL of 5:1 ethanol:water was refluxed overnight. Evaporation of the solvent and aqueous work up provided 33 mg of alcohol **77**, which was used in the next step

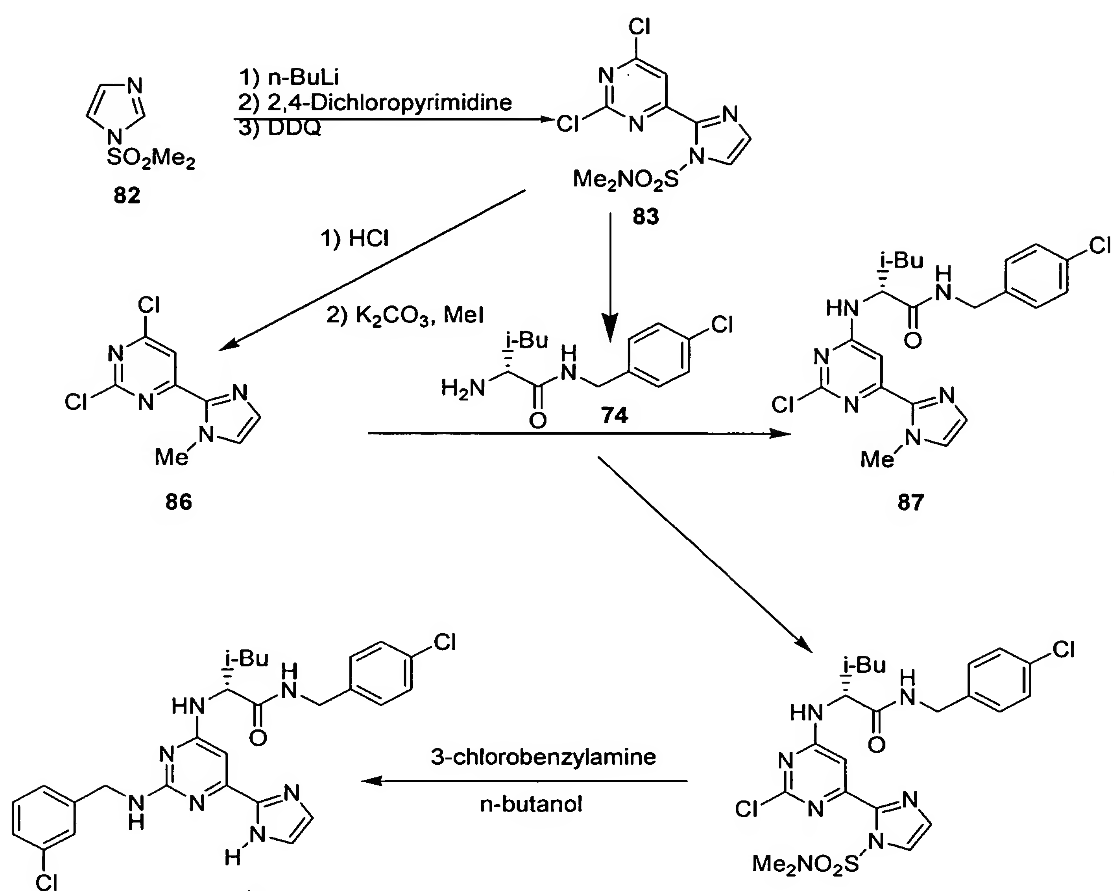
without purification.

A solution of alcohol **77** (140 mg, 0.28 mmol) and Et_3N (85 mg, 0.84 mmol) in 3 mL of dry DMSO was treated with pyridine.SO_3 complex (134 mg, 0.84 mmol) at RT. Aqueous work up gave the aldehyde **78** in almost quantitative yield.

A solution of aldehyde **78** (25 mg, 0.05 mmol), NH_2OMe.HCl (42 mg, 0.5 mmol) and anhydrous NaOAc (41 mg, 0.5 mmol) in 5 mL of ethanol was refluxed overnight. Aqueous work up and chromatography (silica gel, hexane:ethyl acetate, 3:1) gave 10 mg of oxime ether **80**, $(M+H)^+$: 529.2

A mixture of aldehyde **78** (135 mg, 0.27 mmol), toluenesulfonylmethyl isocyanide (TOSMIC) (195 mg, 1 mmol) and K_2CO_3 (138 mg, 1 mmol) in 5 mL of methanol was refluxed for 5 h. Evaporation of the solvent and chromatography (silica gel, hexane:ethyl acetate, 1:2) gave 57 mg of oxazole **81**, $(M+H)^+$: 539.2.

Scheme 10



According to Scheme 10, *n*-BuLi (10 mmol, 4 mL of 2.5 M solution in hexane) was added at -78 °C to a solution of 1-dimethylsulfamoylimidazole (1.75 g, 10 mmol) in 50 mL of dry ether. After stirring for 1 h, the suspension of the anion formed was quickly transferred by a syringe to a suspension of 2,4-dichloropyrimidine (1.49 g, 10 mmol)in 80 mL of dry ether maintained at -30 °C. After stirring at -30 °C for 30 min, the temperature was brought to 0 °C and maintained there for additional 30 min. The reaction mixture was quenched with a mixture of acetic acid (0.64 mL) water (0.1 mL) and THF (2 mL). Immediately afterwards, a solution of DDQ (2.27 g, 10 mmol) in 10 mL of THF was added and the reaction mixture was stirred overnight. After diluting with ethyl acetate (25 mL), the reaction mixture was filtered through celite and the filtrate was washed

with water three times. Finally, a quick wash with ice cold 0.5% NaOH was employed to get rid of the hydroquinone. Evaporation of the solvent and chromatography (silica gel, hexane:ethyl acetate 3:1)provided 550 mg of **83**.

A solution of leucine amide **74** (200 mg, 0.79 mmol), 2,4-dichloro-6-(1-dimethylsulfamoylimidazole-2-yl)pyrimidine (254 mg, 0.79 mmol) and Et_3N (88 mg, 0.87 mmol) in 3 mL of DMF was stirred at RT for 5 days. Aqueous work up and chromatography (silica gel, ethyl acetate) gave 200 mg of **84**, $(M+H)^+$: 540.1.

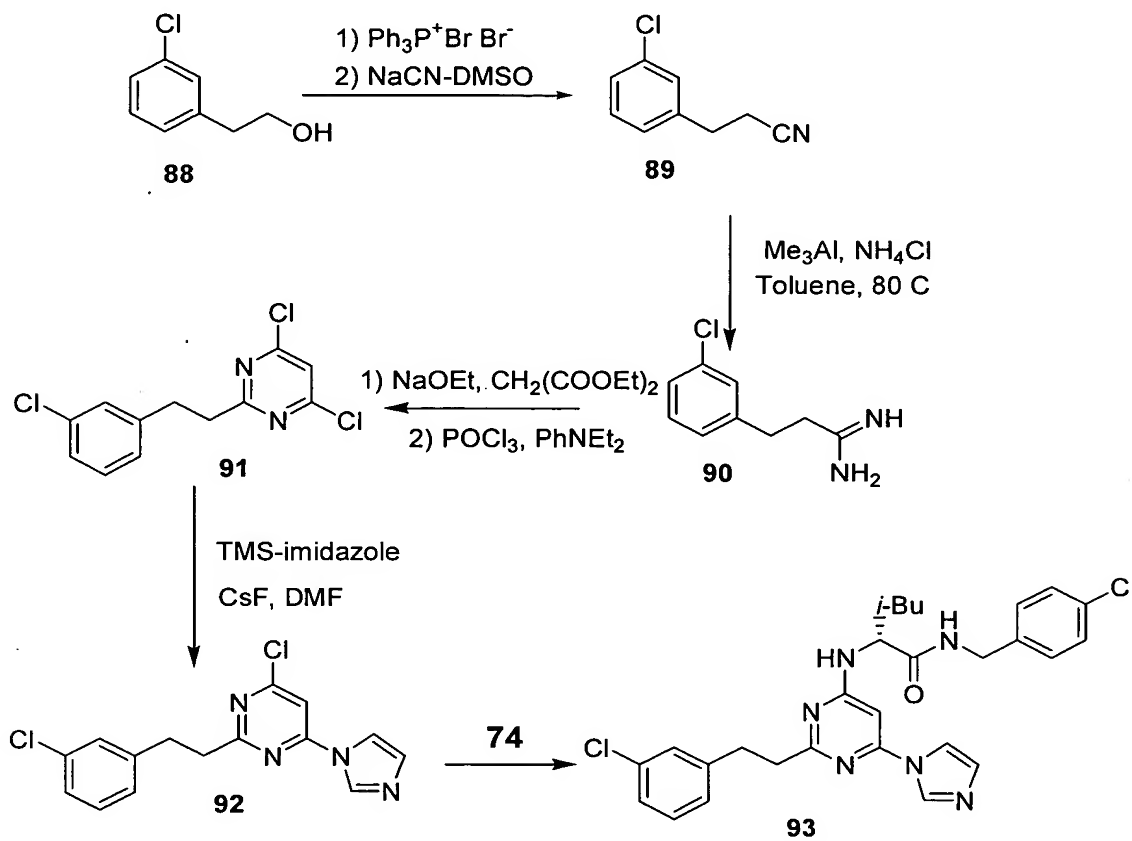
A solution of chloropyrimidine **84** (200 mg, 0.37 mmol) and 3-chlorobenzylamine (568 mg, 4 mmol) in 10 mL of *n*-butanol was refluxed overnight. The solvent was removed *in vacuo* and the residue was chromatographed (silica gel, ethyl acetate:methanol, 98:2) to provide 12 mg of **85**, $(M+H)^+$: 538.2.

A solution of 2,4-Dichloro-6-(1-dimethylsulfamoylimidazole-2-yl)pyrimidine **83** (246 mg, 0.76 mmol) in 10 mL of 1.5 N HCl was refluxed for 1 h. After cooling to RT, the pH was adjusted to 8.5 with aq $NaHCO_3$ and the product was extracted into CH_2Cl_2. After drying the CH_2Cl_2 layer was evaporated to give 110 mg of 2,4-dichloro-6-(imidazole-2-yl)pyrimidine. A mixture of 2,4-dichloro-6-(imidazole-2-yl)pyrimidine (121 mg, 0.56 mmol), K_2CO_3 (100 mg, 0.72 mmol) and CH_3I (2.280 g,1 mL, 16 mmol) in 15 mL of dry acetone was refluxed for 48 h. After cooling to RT, the solvent was evaporated and the residue was partitioned between water and CH_2Cl_2. The CH_2Cl_2 layer was washed successively with water and brine, and then the solvent was evaporated to give 75 mg of 2,4-dichloro-6-(1-methylimidazole-2-yl)pyrimidine **86**.

A solution of 2,4-dichloro-6-(1-methylimidazole-2-yl)pyrimidine **86** (72 mg, 0.31 mmol), leucine amide **74** (100 mg, 0.39 mmol) and Et_3N (100 mg, 1

mmol) in 3 mL of DMF was heated to 70 °C overnight. Aqueous work up and chromatography (silica gel, hexane:ethyl acetate, 1:3) gave 67 mg of **87**, $(M+H)^+$: 447.2.

Scheme 11



According to Scheme 11, a solution of 3-chlorophenethyl alcohol (5 g, 32 mmol) in 50 mL of dry MeCN was treated with dibromotriphenylphosphorane (13.54 g, 32 mmol) for 24 h. The reaction mixture was filtered and the solvent was removed *in vacuo*. The residue was triturated with hexane and filtered. Evaporation of the solvent provided 6.5 g of 3-chlorophenethyl bromide. A solution of the bromide (6.5 g, 29.6 mmol) in 50 mL of dry DMSO containing NaCN (2.17 g, 44 mmol) was heated to 100 °C overnight. The reaction mixture was diluted with water and extracted with ether. The ether layer was washed with water, dried and the solvent was removed *in vacuo*. Chromatography (silica gel, hexane:ethyl acetate, 4:1) provided 3.7 g of nitrile **89**.

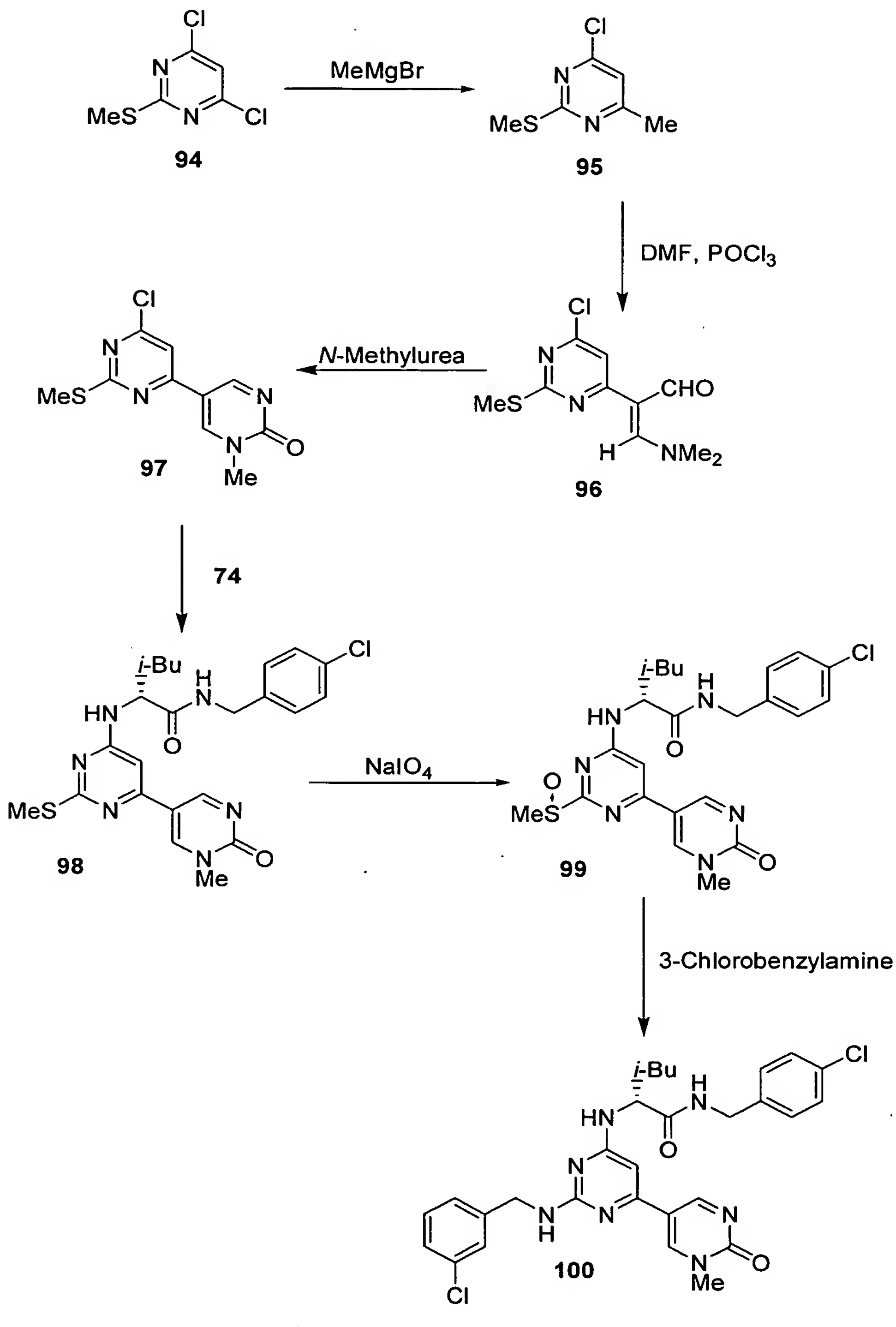
A 2 M solution of Me_3Al in toluene (18 mL, 36 mmol) was slowly added to a stirred suspension of NH_4Cl (2.07 g, 38.7 mmol) in 20 mL of dry toluene at 5 °C. [[6]]After the addition was over, the reaction mixture was warmed to RT and stirred for 2 h. Then, a solution of nitrile **89** (3.7 g, 22.4 mmol) in 15 mL of dry toluene was added and the solution was heated to 80 °C for 18 h. After cooling to RT, the reaction mixture was poured into a slurry of 15 g of silica gel in 50 mL of $CHCl_3$ and stirred for 5 min. The silica gel was filtered and washed with methanol. The filtrate and washings were combined and the solvent was removed. The residue obtained was partitioned between water and methylene chloride. Evaporation of the methylene chloride provided 2.7 g of amidine **90**.

A solution of amidine **90** (2.7 g, 14.8 mmol) and diethyl malonate (2.37 g, 14.8 mmol) in 50 mL of dry ethanol containing freshly prepared NaOEt (1.0 g, 14.8 mmol) was refluxed for 15 h. Afer cooling to RT, the solvent was removed and the residue was dissolved in water. The pH was adjusted to 4 and the precipitated solid was filtered and dried to provide 2.6 g of 2-(3-chlorophenethyl)-4,6-dihydroxy-pyrimidine. A mixture of 2-(3-chlorophenethyl)-4,6-dihydroxypyrimidine (2.6 g, 10.38 mmol), $POCl_3$ (25 mL) and *N,N*-diethylaniline (6 mL) was refluxed overnight. After cooling to RT, the reaction mixture was poured into ice water and the product was extracted into ether. The ether layer was washed successively with water and brine and the solvent was evaporated. Chromatography (silica gel, hexane:ethyl acetate, 9:1) of the oil provided 2.6 g of the 2-(3-chlorophenethyl)-4,6-dichloropyrimidine (**91**).

A solution of 2-(3-chlorophenethyl)-4,6-dichloropyrimidine (286 mg, 1 mmol) **91** in 3 mL of dry DMF was treated with 1-trimethylsilylimidazole (140 mg, 1 mmol) and CsF (152 mg, 1 mmol) at RT overnight. Aqueous work up and chromatography (silica gel, hexane:ethyl acetate, 1:1) gave 200 mg of 4-chloro-2-(3-chlorophenethyl)-6-(1-imidazolyl)pyrimidine (**92**).

A solution of 4-chloro-2-(3-chlorophenethyl)-6-(1-imidazolyl)pyrimidine **92** (100 mg, 0.31 mmol), leucine amide **74** (95 mg, 0.372 mmol) and DIEA (129 mg, 1 mmol) in 2 mL of DMF was heated to 80 °C for 24 h. Aqueous work up and chromatography (silica gel, ethyl acetate:methanol, 98:2) gave 105 mg of **93**, $(M+H)^+$: 537.4

Scheme 12


MeMgBr
DMF, $POCl_3$
N-Methylurea
74
$NaIO_4$
3-Chlorobenzylamine
94
95
96
97
98
99
100

According to Scheme 12, a solution of 4,6-dichloro-2-methylthiopyrimidine (1.95 g, 10 mmol) in 30 mL of dry THF was cooled to 0 °C and treated with a solution of MeMgBr (14 mL of 1.4 M solution, 19.6 mmol). After overnight stirring at RT, the reaction mixture was quenched with sat. NH_4Cl. The organic layer washed with brine, dried and evaporated. The residue was purified by chromatography (silica gel, hexane:ethyl acetate, 9:1) to provide 1.3 g of 4-chloro-6-methyl-2-methylthiopyrimidine (**95**).

Dry DMF (2 mL) was cooled to –5 °C and $POCl_3$ (15.4 mmol, 2.31 g) was added dropwise. The cooling bath was removed and the reaction mixture was stirred for 15 min at RT. 4-chloro-6-methyl-2-methylthiopyrimidine (1.3 g, 7.47 mmol) was added and the contents were heated to 60 °C overnight. The reaction mixture was poured on ice, pH was adjusted to 9 and the precipitated product was filtered. The precipitate was washed with water and dried to provide 1.3 g of the enaminone **96**.

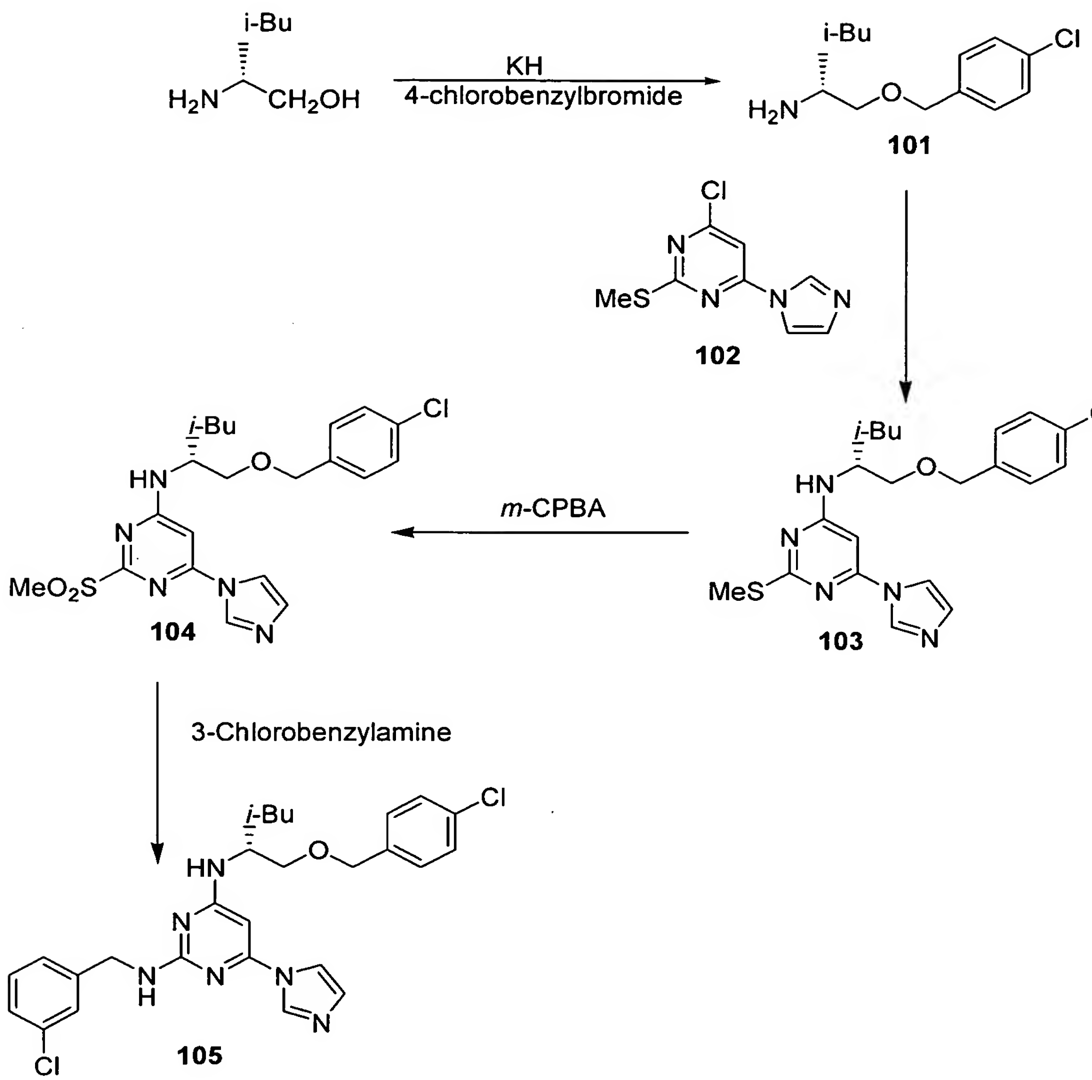
A mixture of enaminone **96** (675 mg, 2.6 mmol) and *N*-methylurea (232 mg, 3.14 mmol) in 5 mL of acetic acid was heated to 100 °C for 2 h. Aqueous work up and chromatography (silica gel, ethyl acetate:methanol, 98:2) gave 100 mg of pyrimidinone **97**.

A solution of **97** (100 mg, 0.37 mmol), leucine amide **74** (100 mg, 0.34 mmol) and DIEA (60 mg, 0.46 mmol) in 3 mL of DMF was heated to 80 °C for 2 days. Aqueous work up followed by chromatography (silica gel, ethyl acetate:methanol, 95:5)gave 30 mg of **98**.

A mixture of **98** (30 mg, 0.061 mmol) and $NaIO_4$ (263 mg, 1.23 mmol) in 6 mL of 1:1 methanol:water was stirred overnight at RT. Aqueous work up gave 10 mg of the crude sulfoxide **99**.

The sulfoxide **99** (10 mg, 0.002 mmol) and 3-chlorobenzylamine (27 mg, 0.2 mmol) in 2 mL of *n*-butanol were heated to reflux for 24 h. Aqueous work up after removal of *n*-butanol, followed by chromatography (silica gel, CH2Cl2:methanol, 95:5) gave 2 mg of **100**, $(M+H)^+$: 580.2.

Scheme 13



i-Bu
H2N
CH2OH
KH
4-chlorobenzylbromide
101
Cl
MeS
102
m-CPBA
MeO2S
104
103
3-Chlorobenzylamine
105

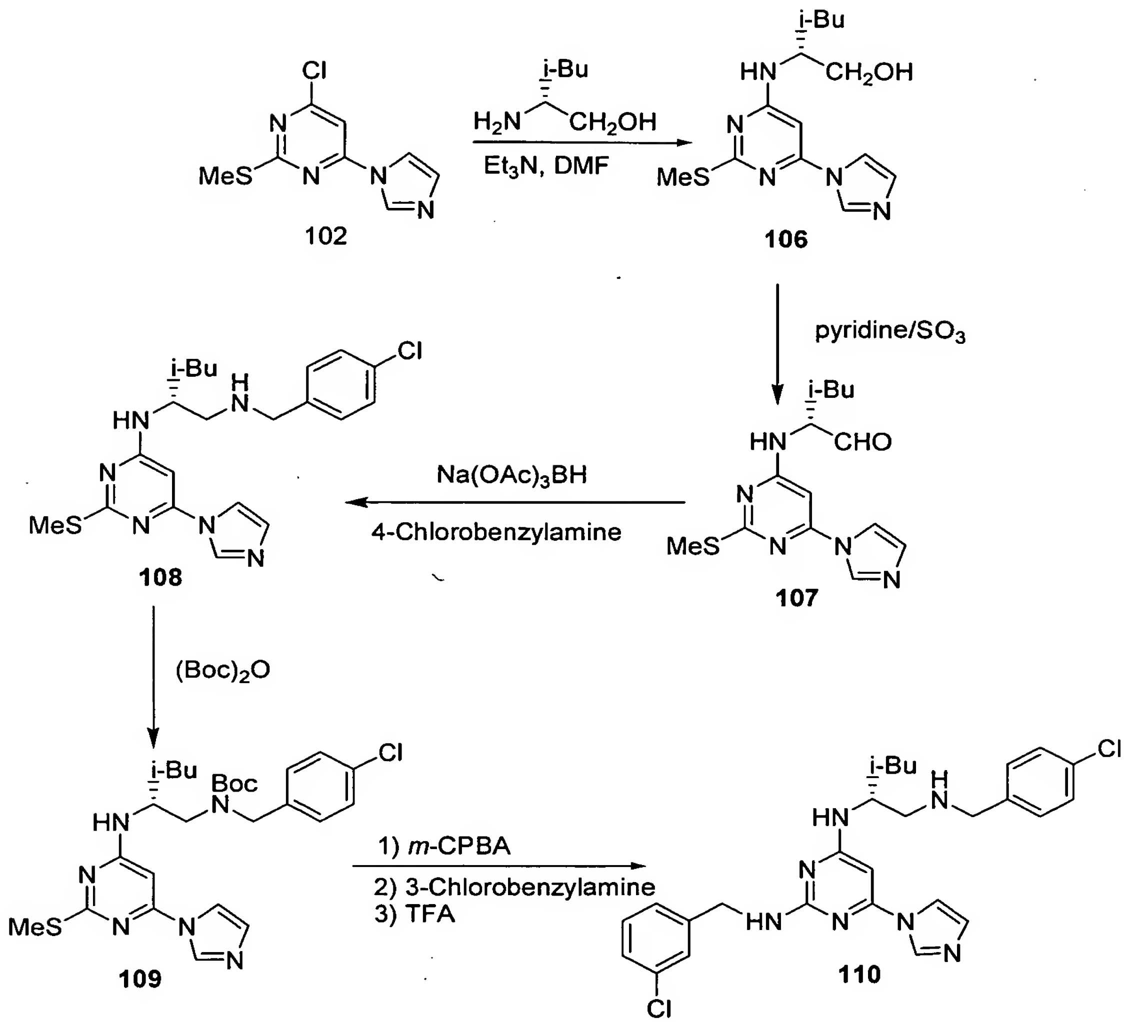
According to Scheme 13, a solution of (*R*)-leucinol (1.288 g, 11 mmol) in 5 mL of THF at RT was added dropwise to a stirred suspension of potassium hydride (0.485 g, 12.1 mmol) in 25 mL of dry THF. After overnight stirring at RT, a solution of 4-chlorobenzylbromide (2.25g, 11 mmol) in 5 mL of THF was added dropwise . The stirring was continued for additional 3 h. The solvent was evaporated and the residue was partitioned between water and ether. The ether layer was washed with brine, dried and the solvent was removed *in vacuo* to provide 2.1 g of ether **101**.

A solution of 4-chloro-6-(1-imidazolyl)-2-methylthiopyrimidine (227 mg, 1 mmol), aminoether **101** (242 mg, 1 mmol) and Et_3N (101 mg, 1 mmol) in 4 mL of DMF was heated to 70 °C for 24 h. Aqueous work up and chromatography (silica gel, hexane:ethyl acetate, 1:1) provided 300 mg of thioether **103**.

A solution of the thioether **103** (300 mg, 0.7 mmol) in 10 mL of CH_2Cl_2 was treated with *m*-CPBA (428 mg, 1.74 mmol) at 0 °C overnight. The precipitate was filtered and the filtrate was evaporated to obtain crude sulfone **104**. No starting material or intermediate sulfoxide was detected by MS.

A solution of sulfone **104** (100 mg, 0.22 mmol) and 3-chlorobenzylamine (2 mmol) in 3 mL of *n*-butanol was refluxed for 24 h. Aqueous work up after removal of *n*-butanol, followed by chromatography (silica gel, ethyl acetate) gave 22 mg of **105**, $(M+H)^+$: 525.2.

Scheme 14


Cl
MeS
N
N
N
N
102
i-Bu
H_2N
CH_2OH
Et_3N, DMF
i-Bu
HN
CH_2OH
MeS
106
pyridine/SO_3
i-Bu
HN
CHO
MeS
107
Na(OAc)$_3$BH
4-Chlorobenzylamine
i-Bu
H
N
Cl
HN
MeS
108
$(Boc)_2O$
i-Bu
Boc
HN
MeS
109
1) m-CPBA
2) 3-Chlorobenzylamine
3) TFA
i-Bu
H
HN
110

According to Scheme 14, a solution of 4-chloro-6-(1-imidazolyl)-2-methylthiopyrimidine (227 mg, 1 mmol) , (*R*)-leucinol (117 mg, 1 mmol) and Et_3N (101 mg, 1 mmol) in 3 mL of DMF was heated to 70 °C for 24 h. Aqueous work up and chromatography (silica gel, hexane:ethyl acetate, 1:3) gave 290 mg of **106**.

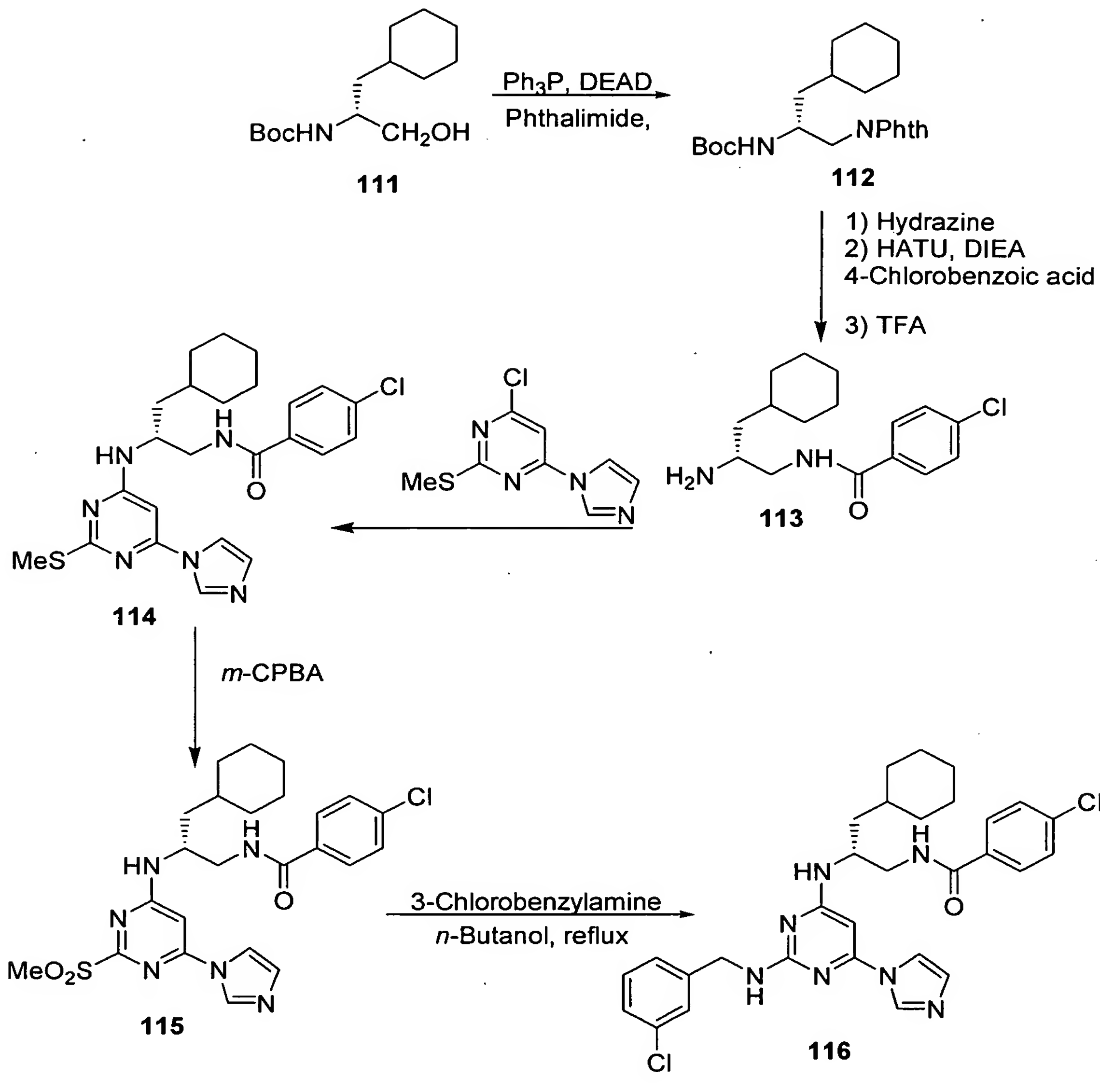
A solution of alcohol **106** (290 mg, 0.94 mmol) and Et_3N (303 mg, 3 mmol) in 5 mL of DMSO was treated with pyridine-sulfur trioxide complex (477 mg, 3 mmol) at RT overnight. Aqueous work up gave 280 mg of the crude aldehyde **107** which was used in the next step without purification..

A mixture of aldehyde **107** (280 mg, 0.91 mmol), $Na(OAc)_3BH$ (290 mg, 1.37 mmol), 4-chlorobenzylamine (142 mg, 1 mmol) and HOAc (60 mg, 1 mmol) in 10 mL of dry 1,2-dichloroethane was stirred at RT overnight. Aqueous work up and chromatography (silica gel, CH_2Cl_2:methanol:NH_4OH, 95:5:0.5) gave 135 mg of **108**.

A solution of amine **108** (130 mg, 0.3 mmol) and boc-anhydride (214 mg, 1 mmol) in 5 mL of THF was stirred at RT overnight. Aqueous work up after removal of the solvent, provided 60 mg of the Boc-protected amine **109**.

A mixture of the Boc-protected amine **109** (60 mg, 0.11 mmol) and *m*-CPBA (83 mg, 0.33 mmol) in 20 mL of 1:1 CH_2Cl_2:phosphate buffer was stirred at 0° C for 2 h and then kept in the refrigerator overnight. The methylene chloride layer was filtered and the solvent was removed to provide the crude sulfone. A solution of the sulfone in 5 mL of *n*-butanol containing 10 eq of 3-chlorobenzyl-amine was refluxed for 20 h. The solvent was removed *in vacuo* and the residue was treated with 2:1 CH_2Cl_2:TFA for two days. After removal of the solvent, the residue was taken in water and basified. The precipitated product was extracted into CH_2Cl_2. Evaporation of the CH_2Cl_2 layer gave 6 mg of **110**, $(M+H)^+$: 524.2.

Scheme 15


BocHN
CH2OH
111
Ph3P, DEAD
Phthalimide,
BocHN
NPhth
112
1) Hydrazine
2) HATU, DIEA
4-Chlorobenzoic acid
3) TFA
H2N
NH
Cl
O
113
Cl
N
MeS
N
N
N
HN
H
N
O
Cl
N
MeS
N
N
N
114
m-CPBA
HN
H
N
Cl
O
N
MeO2S
N
N
N
115
3-Chlorobenzylamine
n-Butanol, reflux
HN
H
N
Cl
O
N
N
H
N
N
N
Cl
116

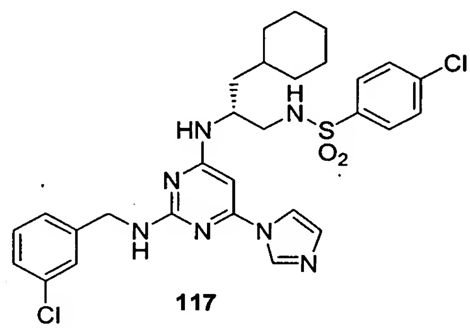
According to Scheme 15, a solution of Ph_3P (262 mg, 1 mmol) and phthalimide (147 mg, 1 mmol) in 3 mL of dry THF was treated with a solution of diethyl azodicarboxylate (174 mg, 1 mmol) in 2 mL of dry THF at RT. After stirring for 5 min, a solution of alcohol **111** (257 mg, 1 mmol) in 5 mL of dry THF was added and the stirring was continued for 3 days. The solvent was removed and the residue was chromatographed (silica gel, hexane:ethyl acetate, 4:1) to obtain 320 mg of phthalimide **112**.

Three hundred twenty milligrams (0.83 mmol) of phthalimide **112** and 50 mg (1 mmol) of $NH_2NH_2.H_2O$ in 5 mL of ethanol was refluxed for 2 h. The solvent was removed and the residue was partitioned between CH_2Cl_2 and 1 N NaOH. Evaporation of the organic layer after drying provided the primary amine. The amine was coupled with 4-chlorobenzoic acid (130 mg, 0.83 mmol) using HATU (1 eq) in DMF containing 2 eq of DIEA. The amide was purified by chromatography (silica gel, hexane:ethyl acetate, 1:1), yield 200 mg. The boc group was removed by stirring in TFA:CH_2Cl_2 (1:2) at RT overnight <u>to provide **113**</u>.

A solution of 4-chloro-6-(1-imidazolyl)-2-methylthiopyrimidine (227 mg, 1 mmol), TFA salt of amine **113** (220 mg, 1 mmol) and Et_3N (303 mg, 3 mmol) in 3 mL of DMF was heated to 80 °C overnight. Aqueous work up and chromatography (silica gel, hexane:ethyl acetate, 1:3) gave 130 mg of **114**.

A solution of the thioether **114** (130 mg, 0.27 mmol) in 20 mL of CH_2Cl_2 was treated with *m*-CPBA (196 mg , 0.8 mmol) at 0 °C for 1 h, and then left in a refrigerator overnight. The reaction mixture was filtered and the crude sulfone **115** was isolated by evaporation of the filtrate.

A solution of sulfone **115** (130 mg, 0.25 mmol) , 3-chlorobenzylamine (72 mg, 0.5 mmol) and Et_3N (50 mg, 0.5 mmol) in 4 mL of *n*-butanol was heated to reflux for 20 h. Aqueous work up and chromatography (silica gel, ethyl acetate:methanol, 99:1) gave 66 mg of **116**, $(M+H^+)$: 578.2.

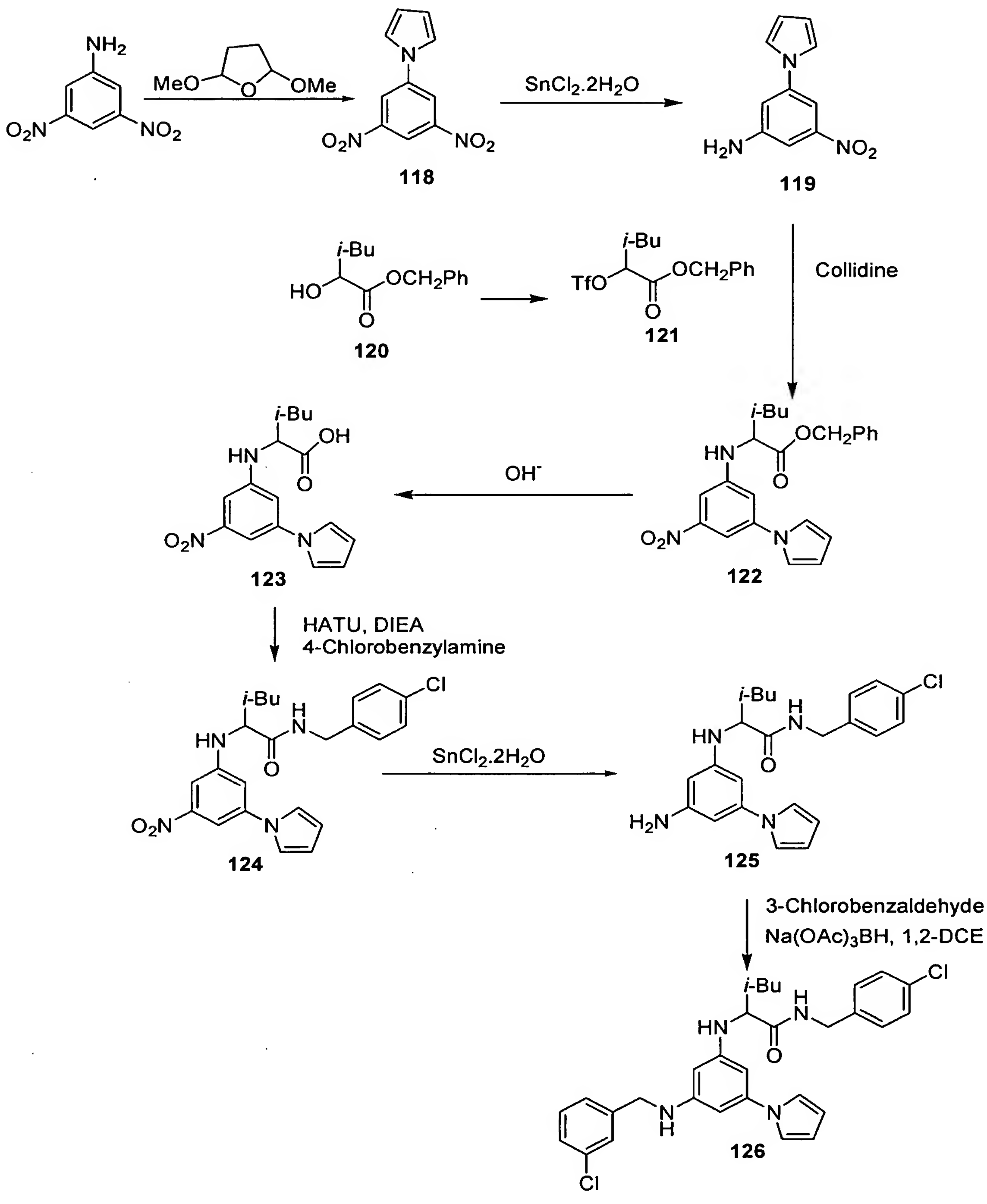


117

The corresponding sulfonamide **117** was prepared by a similar procedure to that of Scheme 15, using 4-chlorobenzenesulfonyl chloride in place of 4-chlorobenzoyl chloride, $(M+H)^+$: 614.2.

Compounds in which X, Y and Z are CH and Q is pyrrole are prepared as shown in Scheme 16

Scheme 16


NH2
MeO
O
OMe
O2N
NO2
118
SnCl2.2H2O
H2N
119
i-Bu
HO
OCH2Ph
120
TfO
121
Collidine
OH
HN
123
OH⁻
122
HATU, DIEA
4-Chlorobenzylamine
Cl
124
125
3-Chlorobenzaldehyde
Na(OAc)3BH, 1,2-DCE
126

According to Scheme 16, a solution of 3,5-dinitroaniline (1.83 g, 10 mmol) and 2,5-dimethoxytetrahydrofuran in 20 mL of HOAc was refluxed overnight. The reaction mixture was poured into water and extracted with EtOAc. The ethyl acetate layer was washed with water followed by aq $NaHCO_3$ and brine. After drying, the solvent was removed to provide 1.52 g of 1-(3,5-dinitrophenyl)pyrrole.

A mixture of 1-(3,5-dinitrophenyl)pyrrole (1.52 g, 6.52 mmol) and $SnCl_2.2H_2O$ (4.4 g, 19.57 mmol) in 30 mL of ethyl acetate was stirred over weekend at RT. The solvent was removed and the residue was taken in water. The aqueous layer was basified with 1 N NaOH to dissolve the tin salts, and the product was extracted into ethyl acetate. Chromatography (silica gel, hexane:ethyl acetate, 4:1) of the crude product provided 440 mg of 1-(3-amino-5-nitrophenyl)pyrrole.

A solution of benzyl ester **120** (222 mg, 1 mmol), DIEA (129 mg, 1mmol) and triflic anhydride (282 mg, 1 mmol) in 5 mL of dry CH_2Cl_2 was stirred at 0 °C for 1.5 h. TLC in hexane:ethyl acetate (4:1) indicated complete conversion of the starting material. The solvent was removed and the crude triflate **121** was used for the next step.

A solution of 1-(3-amino-5-nitrophenyl)pyrrole (203 mg, 1 mmol) and triflate **121** in 15 mL of 1,2-dichloroethane containing collidine (121 mg, 1 mmol) was refluxed for 24 h. Aqueous acidic work up, followed by chromatography (hexane:ethyl acetate, 4:1 gave 95 mg of **122**.

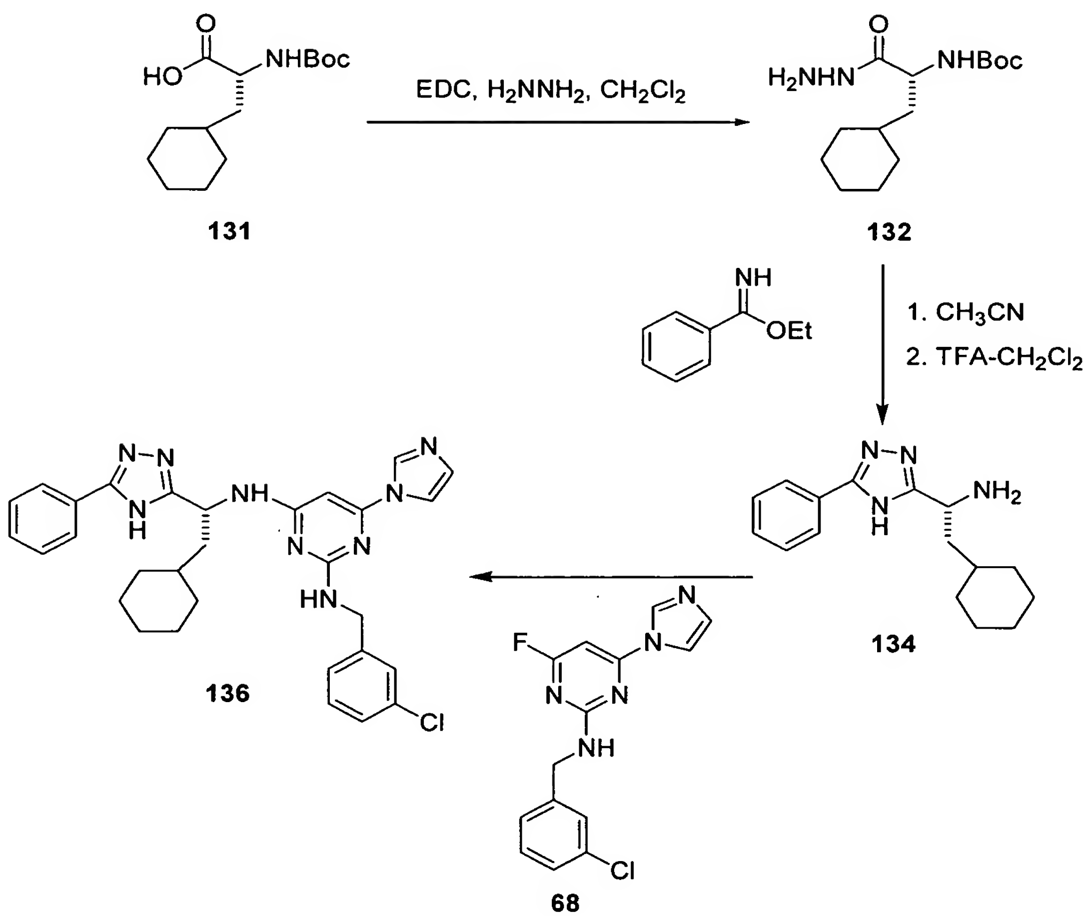
The ester **122** (95 mg, 0.23 mmol) was treated 250 mg of NaOH in 5 mL of 95:5 methanol:water. After overnight stirring at RT, the solvent was removed and the residue was taken in water. The pH was adjusted to 3 and the precipitated acid was extracted into ethyl acetate. Evaporation of the ethyl acetate layer gave 57 mg of **123**.

To a solution of carboxylic acid **123** (57 mg, 0.18 mmol) in 3 mL of dry DMF containing 2 eq of DIEA, 1 eq of HATU was added. After 5 min 1 eq of 4-chlorobenzyl amine was added and the stirring was continued overnight. The crude product **124** obtained after aqueous work up was used directly for the next step.

Amide **124** was reduced with $SnCl_2.2H_2O$ (5 eq) in ethyl acetate as described earlier. The aniline **125** was purified by chromatography (silica gel, hexane:ethyl acetate, 1:1), yield 7 mg.

A mixture of aniline **125** (7 mg, 0.017 mmol), $Na(Oac)_3BH$ (6 eq) and 3-chlorobenzaldehyde (6 eq) in 2 mL of 1,2-dichloroethane was stirred at RT overnight. Aqueous work up and chromatography (silica gel, hexane: ethyl acetate, 62:38) gave 3 mg **126**, $(M+H)^+$: 535.1.

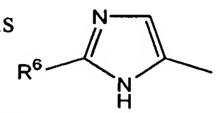
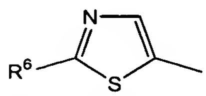
Scheme 17



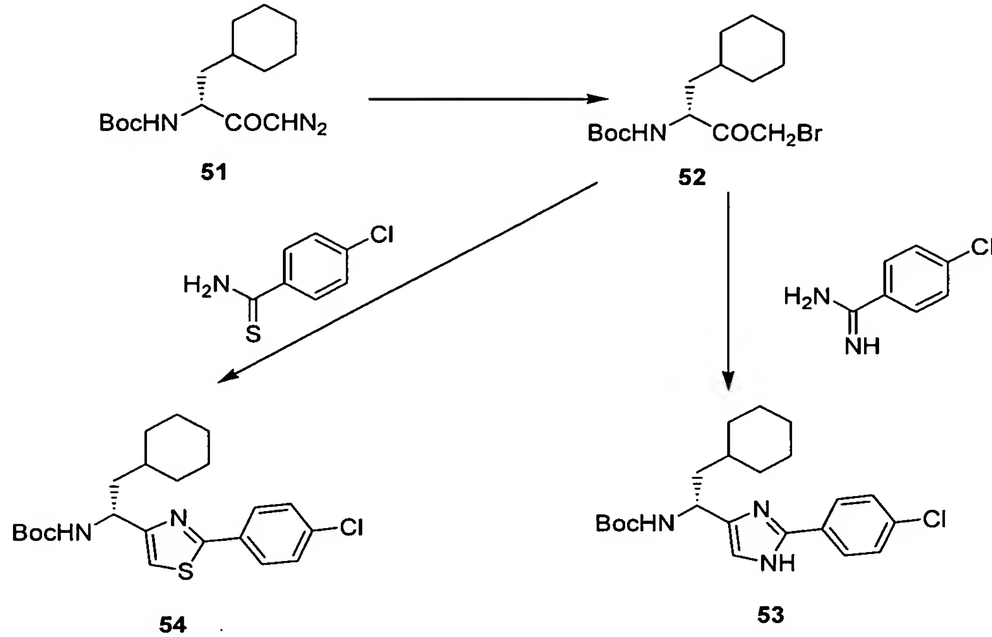
To a solution of N-BOC-cyclohexyl alanine (200 mg, 0.74 mmol) in 2 mL of dry methylenechloride was added dropwise hydrazine (0.1 mL, 0.89 mmol) and EDC (159 mg, 0.81 mmol) at 23 °C. The reaction mixture was stirred for 48 h, then washed with NH_4Cl, water, and brine to give 150 mg of **132**.

A solution of hydrazide **132** (72.4 mg, 0.254 mmol) and imidate **133** (52 mg, 0.28 mmol) in 2 mL of dry acetonitrile was stirred for 16 h at RT. TLC .indicated complete absence of the starting material. Solvent was removed and the crude product was treated with TFA:methylenechloride, 1:1, and washed with 1 N NaOH, water and brine to give 16.2 mg of the triazole **134**.

A solution of triazole **134** (16.2 mg, 0.06 mmol), fluoropyrimidine **68** (27.3 mg, 0.09 mmol) and iPr_2NEt (0.02 mL, 0.12 mmol) in 1 mL of dry nBuOH was refluxed for 16 h. Evaporation of the solvent, followed by aqueous work up and chromatography (silica gel, hexane:ethyl acetate:methanol, 4:4:1) gave 9.0 mg of the desired product **136**.

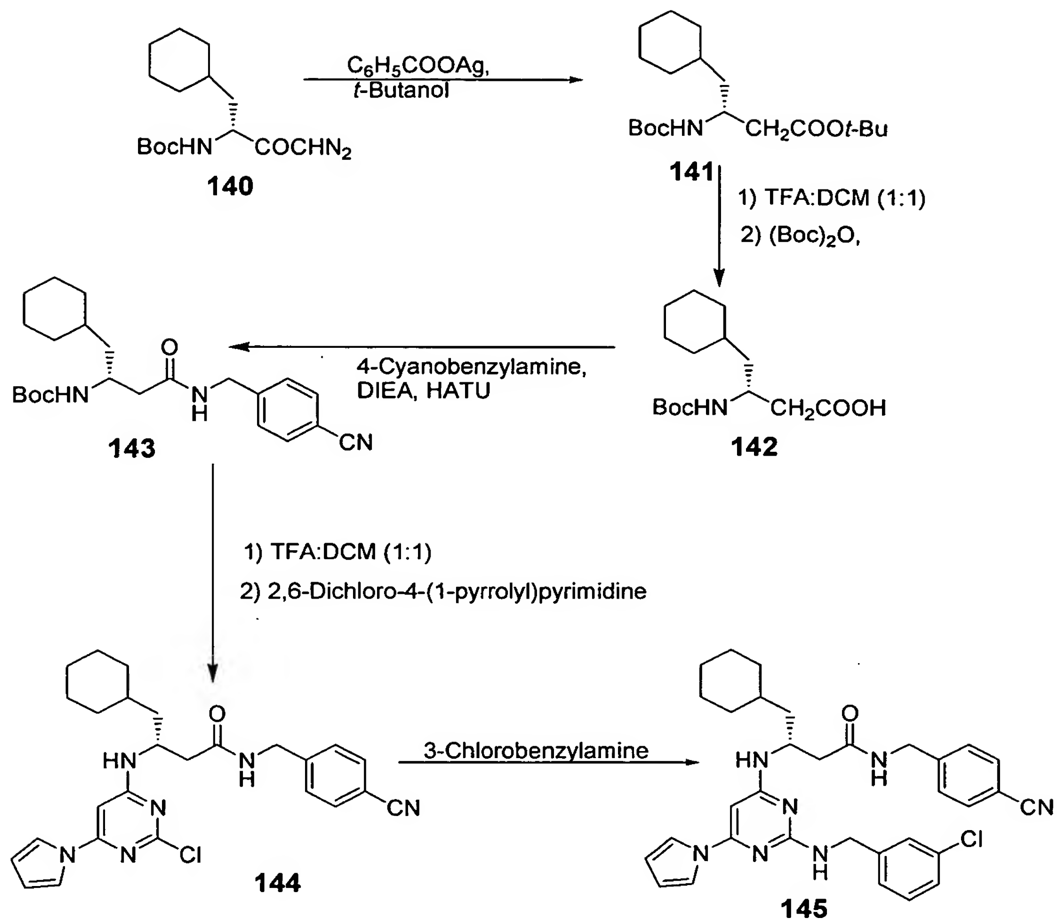
Compounds of the invention in which A^1 is  and in which A^1 is  are synthesized as shown in Scheme 17. In both cases the Boc protecting group is cleaved with trifluoroacetic acid and the amine is reacted further as already described.

Scheme 18



A solution of diazo ketone **51** (2.89 g, 9.78 mol.) in 60 mL of ether was cooled to -20°C and 2 mL of 48% HBr (960 mg, 11.85 mol.) was added dropwise. After 35 minutes, an additional 0.5 mL of HBr (240 mg, 2.96 mol.) was added and the stirring was further continued for 25 min. TLC [hexane:ethyl acetate (4:1)] indicated complete absence of the starting material and appearance of the less polar α-bromoketone. Cold aqueous work-up and chromatography on silica gel with hexane:ethyl acetate (85:15) gave 2.7 g of the pure α-bromoketone **52**. ^{1}H NMR ($CDCl_3$): 5.00-4.80 (m, 1H), 4.64-4.50 (m, 1H), 1,90-0.90 (m, 22H). The α-bromoketone is reacted with 4-chlorobenzamidine in refluxing chloroform to provide the imidazole **53** according to the method of Nagao et al. [Heterocycles 42, 517-523 (1996)]. The α-bromoketone is reacted with 4-chlorothiobenzamide in dioxane to provide the thiazole **54** according to the method of Nan'Ya et al.[J. Heterocycl. Chem. 32, 1299-1302 1995].

Scheme 19



Scheme 19 illustrates the synthesis of an example in which m is 1. A solution of Boc-α-cyclohexyl-D-alanine (1.085 g, 4.0 mmol) and *N*-methylmorpholine (404 mg, 4.0 mmol) in 15 mL of dry THF was cooled to –10 °C and a solution of isobutyl chloroformate (544 mg, 4.0 mmol) in 5 mL of THF was added dropwise. After stirring for additional 10 min, an ethereal solution of diazomethane (*ca.* 9 mmol) was added slowly. After overnight stirring at RT, TLC indicated formation of diazoketone($R_f \approx 0.4$ in hexane: ethyl acetate 4:1). The excess diazomethane was destroyed by addition of aq HOAc and the solvent was evaporated *in vacuo*. The residue obtained was partitioned between ether and water. The ether layer was successively washed with aq $NaHCO_3$, water and brine. After drying ($MgSO_4$), the ether was evaporated to give the diazoketone **140** as a

pale yellow oil.

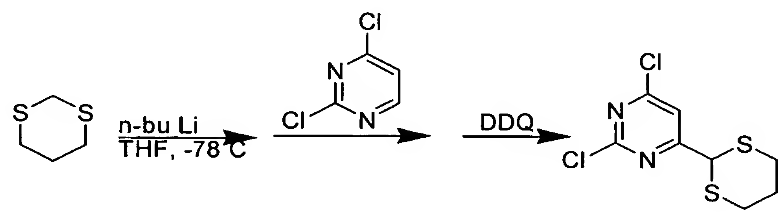
The diazoketone was dissolved in 10 mL of *t*-butanol and the solution was brought to reflux under argon. A freshly prepared and filtered solution of silver benzoate (0.5 g, 2.18 mmol) in 3 mL of Et_3N was added dropwise over 30 min *via* syringe. The reflux was continued for an additional 1 h. A small amount of decolorizing carbon was added and the reaction mixture was filtered through celite. After evaporation of the filtrate, the residue was chromatographed (silica, hexane:ethyl acetate (85:15)) to give 650 mg of *R*-*t*-butyl 3-(cyclohexylmethyl)-3-*t*-butoxycarbonylaminopropionate, **141** $(M+H)^+$: 342.0.

A solution of **141** (650 mg, 1.90 mmol)) in 10 mL of TFA:DCM (1:1) was stirred for 6 h at RT. The solvent was removed and the residue was treated with Boc-anhydride in dioxan-aq NaOH to give 486 mg of *R*-3-(cyclohexylmethyl)-3-*t*-butoxy carbonylamino-propionic acid, **142** $(M-H)^+$: 284.7

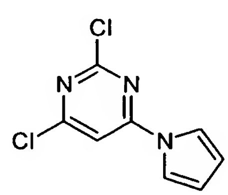
A solution of **142** (284 mg, 1.0 mmol) and DIEA (258 mg, 2.0 mmol) in 5 mL of dry DMF was treated with HATU (380 mg, 1 .0 mmol) at RT. After 5 min, 4-cyanobenzylamine (132 mg, 1.0 mmol) was added and the reaction mixture was stirred overnight at RT. Aqueous workup and chromatography (silica gel, hexane:ethyl acetate (1:3) gave 200 mg of the amide **143**.

A solution of the amide **143** (200 mg, 0.5 mmol) in 10 mL of TFA:DCM (1:1) was stirred at RT for two days. The solvent was evaporated and the residue was taken in 5 mL of DMF containing DIEA (258 mg, 2.0 mmol) and 2,6-dichloro-4-(1-pyrrolyl)pyrimidine (107 mg, 0.5 mmol). After heating overnight at 80 °C, the reaction mixture was diluted with water and the product was extracted into ethyl acetate. The solvent was removed and the residue was chromatographed (silica gel, hexane:ethyl acetate (1:3)) to give 50 mg of the 2-(1-pyrrolyl)pyrimidine derivative and 58 mg of the 4-(1-pyrrolyl)pyrimidine compound **144**, $(M+H)^+$: 477.3

A solution of **144**, (30 mg, 0.063 mmol) and 3-chlorobenzylamine (50 mg, 0.35 mmol) in 2 mL of *n*-butanol was refluxed overnight. The solvent was removed and the residue was purified by chromatography (silica gel, hexane:ethyl acetate (1:3)) to give 4 mg of **145,** $(M+H)^+$: 582.3



To 1,3-dithiane (6.2g, 50.0 mmol) in 20 mL dry THF was added n-butyl lithium (2.5M, 22mL, 55.0 mmol) dropwise while cooling to -78°C. After 30 minutes a solution of 2,4-dichloropyrimidine (10.0g, 75 mmol) in 15 mL dry THF was added dropwise. After 30 minutes the mixture was warmed to 0° and DDQ (12.5g, 55.0 mmol) was added and allowed to warm to room temperature. After 1 hour the mixture was concentrated and the resulting residue purified on a silica gel column, eluting with 3:7 EtOAc:hexanes to yield 2,4-dichloro-6-(2-dithianyl)pyrimidine as a light yellow oil (1.2g, 5.5 mmol, 9%)



2,6-Dichloro-4-(1-pyrrolyl)pyrimidine was prepared as follows: A dry 500 mL round bottom flask (oven-heated/argon cooled), was charged with 2.97 g (74.34 mmol) of a 60% dispersion of sodium hydride in mineral oil. The flask was purged with argon, and 200 mL of hexane were quickly added. The mixture was purged again, and stirred for 5-10 minutes. The stirring was then stopped, and the sodium hydride was allowed to settle, at which point the hexane was quickly decanted off. The mixture was purged with argon again and the rinsing was

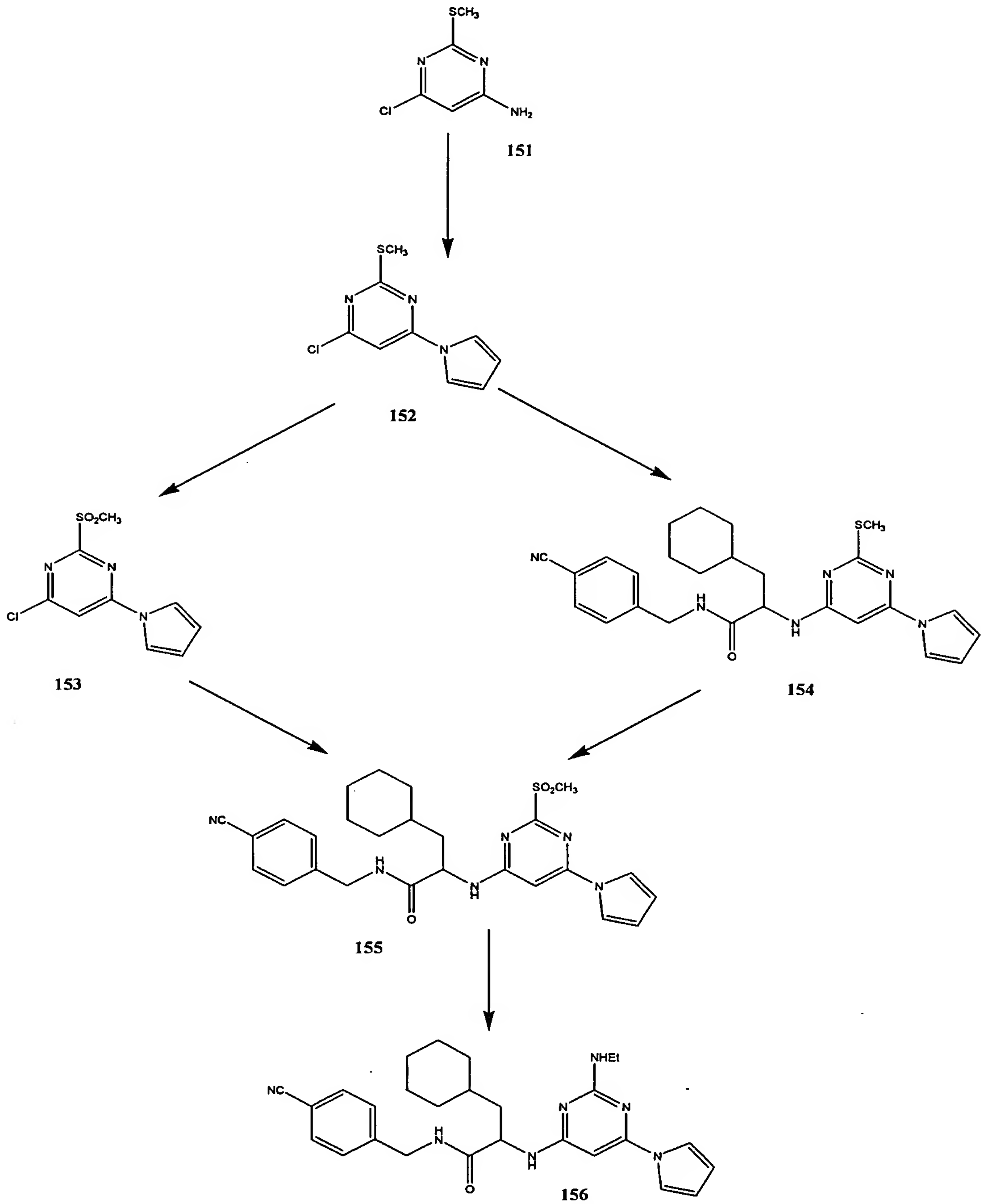
repeated, to ensure the reaction is free from the mineral oil suspension. Next, 200 mL of dry THF were injected by syringe into the air-free mixture. The mixture was then cooled to 0°C, and connected to an oil-bubbler. Then 3.44 mL (49.60 mmol)of pyrrole were injected into the mixture by syringe (vigorous bubbling occurred as hydrogen evolved), and it was stirred for 1 hr. Finally, 10 g (54.52 mmol)of 2,4,6-trichloropyrimidine were injected quickly into the reaction mixture, and it was vigorously stirred overnight. The reaction mixture was diluted with 200 mL of ethyl acetate and washed with a solution of 14.5 g (75 mmol), of citric acid in 100 mL of water. The organic layer was extracted and dried with magnesium sulfate. The mixture was then concentrated down to give a brown, viscous material. The crude material was loaded relatively quickly onto a chromatographic column (25''x 3''), which was filled with 11 ¼'' silica gel. Elution was started at 40:1 hexane/ether for about 2 L, and then the concentration was increased to 35:1 hexane/ether for about 4 L. The best TLC system was 9:1 hexane/ether. With that system, the four product spots could be seen: the top spot was the regio-isomer with the pyrrole substituted on the 2-position of the pyrimidine, the second spot was unreacted pyrimidine, the third spot was the regio-isomer with the pyrrole substituted at the 4-position (desired product), and the most polar spot was a bis-addition product. Most of the desired product was separated with the column (2.5 g), but the remaining mixture with the bis-product was recrystallized from hexane to give another 1.5 g. The total yield was 4 g (38%) of the white solid. ^{1}H NMR in $CDCl_3$: a 2H triplet at 6.42 ppm (j=2.55 Hz), a 1H singlet at 7.16 ppm, and a 2H triplet at 7.48 ppm (J=2.55 Hz). In 9:1 hexane/ether, the R_f= 0.37. This compound did not give a mass spec signal.

The corresponding 2,6-difluoro-4-(1-pyrrolyl)pyrimidine is made in analogous fashion from 2,4,6-trifluoropyrimidine. Both are useful as intermediates in the synthesis of B_1-BK antagonists of the invention. An improved synthesis of 2,6-dichloro-4-(1-pyrrolyl)pyrimidine proceeds from 4-amino-2,6-dichloropyrimidine. A mixture of 4-amino-2,6-dichloropyrimidine (5.0 g, 30.5 mmol) and 2,5-dimethoxytetrahydrofuran (4.03 g, 30.5 mmol) in 100 mL of HOAc

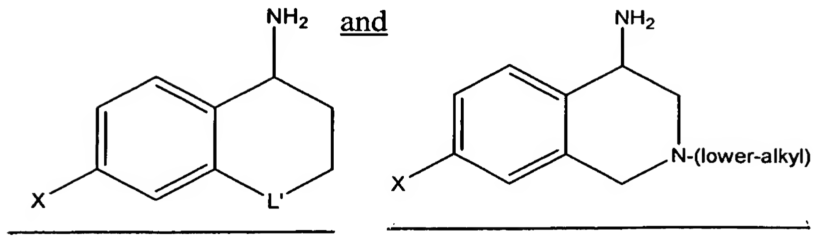
was refluxed for 2 hours. The reaction mixture was cooled to RT and poured into large quantity of water. The crude product was extracted into ethyl acetate and the ethyl acetate layer was extracted successively with water, aqueous $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by chromatography (silica gel, hexane:ethyl acetate (96:4) to provide 4.4 g (73%) of 2,6-dichloro-4-(1-pyrrolyl) pyrimidine. ^{1}H NMR ($CDCl_3$): δ (ppm) 6.4 (s,2H), 7.15 (s, 1H), 7.5 (s, 2H).

As described above, both the dichloro and the difluoro-intermediates provide mixtures of regioisomers when reacted with nucleophiles (cf. **144** in Scheme 19). Although this is useful when both regioisomers are desired, the route shown in Scheme 20 below provides a regioselective synthesis. According to Scheme 20, 4-amino-6-chloro-2-methylthiopyrimidine **151** was reacted with 1 equivalent of 2,5-dimethoxytetrahydrofuran in refluxing acetic acid to provide 6-chloro-2-methylthio-4-(1-pyrrolyl)pyrimidine **152**: ^{1}H NMR ($CDCl_3$) δ 2.75 (s,3H), 6.55 (d,2H), 7.05 (s,1H), 7.65 (d,2H). The 6-chloro-2-methylthio-4-(1-pyrrolyl)pyrimidine **152** is either (a) oxidized with 2.2 equivalents of m-chloroperoxybenzoic acid in dichloromethane at 0°C to provide 6-chloro-2-methylsulfonyl-4-(1-pyrrolyl)pyrimidine **153** or (b) reacted with 1 equivalent of the N-(p-cyanobenzyl)amide of cyclohexylalanine and 1 equivalent of diisopropylethylamine in DMF at 80°C to provide the 2-methylthiopyrimidine **154**. The oxidation and nucleophilic displacement steps are then reversed [i.e. **153** is reacted according to (b) or **154** is reacted according to (a)] to provide the 2-methylsulfonylpyrimidine **155**, which is dissolved in n-butanol saturated with ethylamine and heated in a sealed tube to produce **156**.

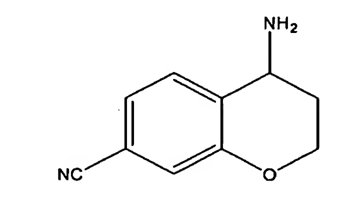
Scheme 20



Compounds of formulae



wherein X is -CN or halogen and L' is -O-, $-CH_2-$ or $-N(CH_3)-$ are useful intermediates for the preparation of compounds of preferred subgenera. Exemplary syntheses are shown below.

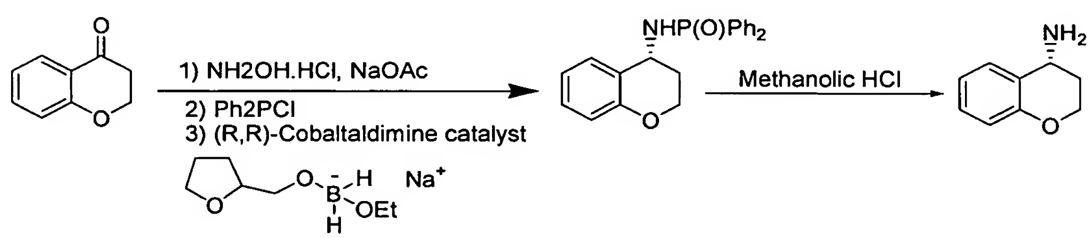


7-Cyano-4-chromanylamine was prepared as follows:

A dry, 250mL round bottom flask was charged with 0.27g (1.01 mmol) of triphenylphosphine, 0.73g (11.15 mmol) of potassium cyanide, 0.22g (3.38 mmol) of zinc dust, and 0.38g (0.51 mmol) of bis(triphenylphosphine)nickel (II) bromide. The flask was then purged with argon, and an air-free solution of 3g (10.14 mmol) of 7-(((trifluoromethyl)sulfonyl)oxy)-4-chromanone [Koch et al., J. Org. Chem. 59, 1216 (1994)] in 40ml of dry acetonitrile was introduced by syringe. The solution was then heated at 60°C for 3 hours, under argon. After cooling the solution to room temp, the solution was added to an equal volume of water. The organic layer was extracted out, and the aqueous layer was extracted several times with ethyl acetate and ether. The combined organic phase was dried over magnesium sulfate, filtered and evaporated. The crude mixture was chromatographed using a 20% ethyl acetate/hexane solvent system which yielded 1.3g (76%) of 7-cyano-4-chromanone as a white solid.

A dry, 200mL round bottom flask was charged with 0.85g (4.83 mmol) of 7-(cyano)-4-chromanone, 3.72g (48.30 mmol) of ammonium acetate, and 0.91g (14.45 mmol) of sodium cyanoborohydride. The flask was then purged with argon, and 30 mL of dry methanol was added by syringe. The solution was stirred at room temp for 48 hours. Concentrated HCl was slowly added dropwise until pH <2 was reached. The methanol was then evaporated by rotovap, and 30 mL of water was added to the suspension, which was then washed 3 times with ethyl acetate. The pH was then brought to > 10 by adding sodium hydroxide pellets to the stirring aqueous mixture. Saturated sodium chloride was added, and the mixture was then extracted several times with ether and ethyl acetate. The combined organic phase was dried over magnesium sulfate, filtered and evaporated to give 0.51g (60%) of the desired 7-(cyano)-4-chromanylamine as a pale yellow oil.

Characterization: The ^{1}H NMR in $CDCl_3$ (using a Varian Gemini 2000 model NMR coupled to a 300 Mz Oxford Magnet) gave the following signals: a broad 2H singlet at 1.6 ppm, a 2H multiplet from 1.8-2.2 ppm, a 1H triplet at 4.05 ppm (J=6 Mz), a 2H multiplet from 4.2-4.4 ppm, a 1H singlet at 7.1 ppm, a 2H doublet at 7.15 ppm (J=12 Mz), and a 2H doublet at 7.45 ppm (J=12 Mz).



A mixture of 4-chromanone (5 g, 33.7 mmol), hydroxylamine hydrochloride (2.34 g, 33.7 mmol and NaOAc (2.766 g, 33.7 mmol) in 100 mL of ethanol was refluxed for 18 h. After cooling to RT, the solvent was removed and the residue was partitioned between water and EtOAc. The EtOAc layer was dried ($MgSO_4$), and the solvent was removed . The solid obtained was triturated with hexane and filtered to provide 4.1 g of 4-hydroxyiminochroman.

A solution of 4-hydroxyiminochroman (783 mg, 4.8 mmol) and triethylamine (484 mg, 4.8 mmol) in 120 mL of dry 1:1 DCM:hexane was cooled to –50 °C. Chlorodiphenylphosphine (1.059 g, 4.8 mmol) was added *via* syringe and the mixture was allowed to stir at –50 °C for 2 h. The mixture was cooled to -78 °C and filtered quickly under N_2 in a glove bag. The filtrate was evaporated and the crude *N*-diphenylphosphinylimine was taken directly to the next step.

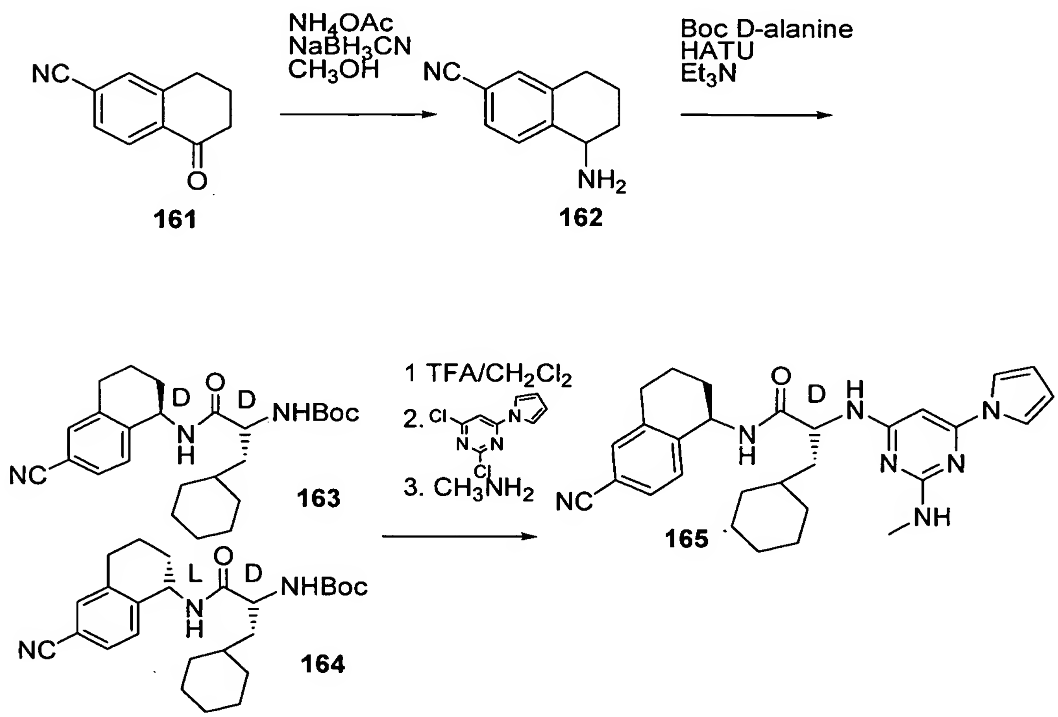
Formation of pre-modified borohydride: Under Ar atmosphere , in a pre-cooled flask at 0 °C were placed 290 mg of $NaBH_4$ (7.5 mmol), 50 mL of $CHCl_3$, and 0.44 mL of EtOH (7.5 mmol) and 10 mL of tetrahydrofurfuryl alcohol. The mixture was stirred for 3 h at 0 °C.

Catalytic borohydride reduction: While maintaining solution of pre-modified borohydride at 0 °C, its solution was slowly added to the solution of 37 mg of (1R,2R)-*N*, *N*'-Bis[3-oxo-2-(2,4,6-trimethylbenzoyl)butylidene]-1,2-diphenylethylenediaminato cobalt(II) (0.05 mmol, 1 mol%, TCI America) and the aforementioned phosphinylimine in 50 mL of $CHCl_3$. The stirring was continued for 4 h at 0 °C. The reaction was quenched by addition of saturated NH_4Cl and extracted with ether. The organic layer was dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by chromatography (silica, hexane:EtOAc, 1:3) to provide 300 mg of the diphenylphosphorylamine. $(M+H)^+$: 350.1.

The diphenylphosphorylamine (300 mg, 0.86 mmol) was dissolved in MeOH saturated with HCl gas and stirred overnight at RT. The solvent was removed and the residue was partitioned between water and ether. The aqueous layer was basified and the liberated amine was extracted into ether. The ether layer was evaporated after drying (K_2CO_3) to provide (*R*)-4-aminochroman. The

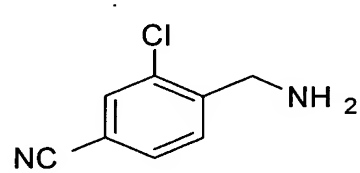
stereochemistry was assigned based on the literature precedence (Sugi, K. D.; Nagata, T.; Mukaiyama, T. Chem. Lett. 1997, 493-494) and the optical purity was found to be > 95% by chiral hplc. ^{1}H NMR ($CDCl_3$): δ 1.75 (bs, 2H, NH_2), δ 1.95-2.05 (m, 1H, CH_2CH_2O), δ 2.30-2.40 (m, 1H, CH_2CH_2O), δ 4.2 (t, 1H, $CHNH_2$), δ 4.35-4.50 (m, 2H, CH2O), δ 7.0 (d, 1H, ArH), δ 7.10 (t, 1H, ArH), δ 7.30 (t, 1H, ArH), δ 7.50 (t, 1H, ArH).

Scheme 21



According to Scheme 21 $NaCNBH_3$ (264 mg, 4.2 mmol) was added to a mixture of **161** (340 mg, 1.99 mmol) [Almansa et al. Synth. Commun. 23, 2965 (1993)] and NH_4OAc (1.5 g, 19.9 mmol) in dry methanol (30 ml), and the reaction was stirred at room temperature for a week. Removed solvent under vacuum. The residue was separated by silica gel chromatography column with methanol/ammonium hydroxide/ethyl acetate (15:1:84) to give 290 mg (84%) of 7-cyano-1,2,3,4-tetrahydronaphthylene-1-amine (**162**). NMR ($CDCl_3$): δ 1.66 – 2.12 (4H, CH_2x2), 2.78 (2H, CH_2), 4.0 (1H, CH), 7.37 (1H, ArH), 7.44 (1H, ArH), 7.54 (1H, ArH).

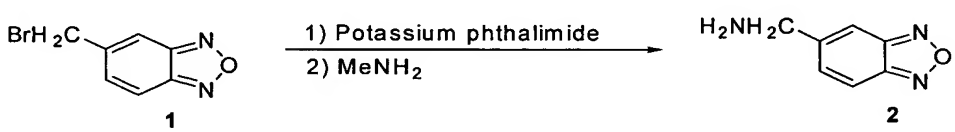
To a solution of 7-cyano-1,2,3,4-tetrahydronaphthylene-1-amine (**162**) (290mg, 1.69 mmol), and Et_3N (427mg, 4.22mmol) in DMF was added HATU (703mg, 1.85 mmol) in one portion with stirring. The reaction was stirred at room temperature overnight, then solvent was removed in vacuo. Chromatographic purification with EtOAc/hexane (3:7) gave 145 mg (20%) of **163** and 151 mg (21%) of **164**. The more polar diasteroisomer **163** was converted into final compound **165** as described earlier.



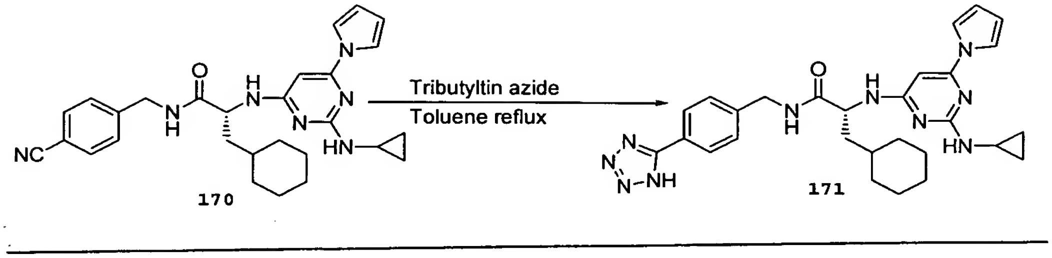
2-Chloro-4-cyanobenzylamine was prepared as follows: To a stirred solution of 2-chloro-4-cyanotoluene (10g, 65.8 mmol) in dry carbon tetrachloride (150ml) were added N-bromosuccinimide (12.9g, 72.4 mmol) and a catalytic amount of benzoyl peroxide. The reaction was refluxed under stirring for 4 h and then filtered. Removed solvent from filtrate in vacuo. The residue, 2-choro-4-cyanobenzyl bromide, was purified by chromatography with EtOAc/hexane.

To a stirred solution of 2-choro-4-cyanobenzyl bromide (6.9 g, 30.0 mmol) in DMF (150 ml), was added sodium azide (2.0g, 30 mmol) The reaction was stirred overnight at room temperature, and then filtered. The DMF was removed from filtrate in vacuo. The residue was dissolved in EtOAc (300 ml), washed with water (200ml x 3), brine (200ml x 1), dried over sodium sulfate. Removed solvent in vacuo to give 5.8g of raw 2-choro-4-cyanobenzyl azide.

To a solution of 2-choro-4-cyanobenzyl azide (5.8g, 30.1 mmol) in THF/H_2O (3:1), was added triphenyl phosphine (12.3g, 46.7 mmol). The reaction was stirred at room temperature overnight, then neutralized with 1N sodium hydroxide, extracted with ethyl acetate (150ml x 3). The organic layer was dried over sodium sulfate, and then solvent was removed in vacuo. The product was purified by silica-gel chromatography column with methanol/ammonia hydroxide/ethyl acetate (20:1:69) to give 4.5g (90%) of 2-chloro-4-cyanobenzylamine. NMR ($CDCl_3$): δ 4.0 (s, 2H, CH_2), 7.58 (d, 2H, HAr), 7.62 (s, 1H, HAr)

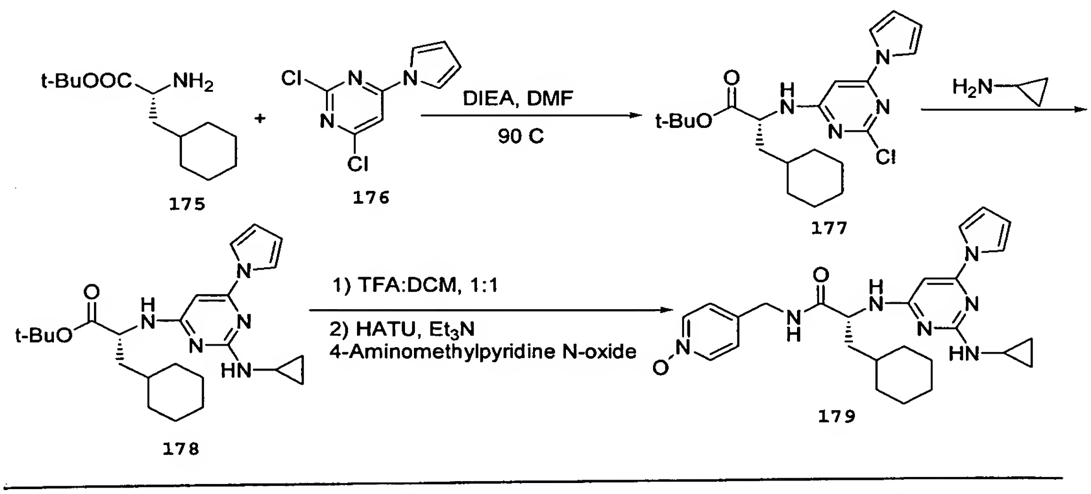


5-Aminomethylbenzofuroxan was prepared as follows: 5-Bromomethylbenzofuroxan (2.13 g, 10 mmol, Gasco, A. M.; Ermondi, G.; Fruttero, R.; Gasco, A. *Eur. J. Med. Chem.* **1996**, 31, 3-10) was dissolved in DMF and treated with potassium phthalimide (1.85 g, 10 mmol) at RT for 15 h. After diluting with water, the product was filtered and crystallized from EtOAc to provide 700 mg of the phthalimide. The phthalimide was suspended in a mixture of 5 mL of ethanol and 5 mL of 40% aq. methylamine, and the reaction mixture was stirred for 2 days at RT. The solvent was removed *in vacuo* and the residue was taken in ether. The ether layer was dried ($MgSO_4$) and the solvent was removed to yield 110 mg of 5-aminomethylbenzofuroxan. ^1H NMR ($CDCl_3$): δ 1.8 (bs, 2H, NH_2) δ 4.1(s, 2H, CH_2), δ 7.5 (d, 1H, ArH), δ 7.8-8.0 (m, 2H, ArH).



A solution of the nitrile **170** (100 mg, 0.2 mmol) and tributylstannyl azide (133 mg, 0.4 mmol) in toluene was refluxed for two days. The solvent was evaporated and the residue was treated with 6 N HCl overnight. After aqueous work up, the tetrazole **171** was purified by chromatography (silica, DCM:MeOH, 95:5). Yield: 35 mg. $(M+H)^+$: 527.3

Scheme 22

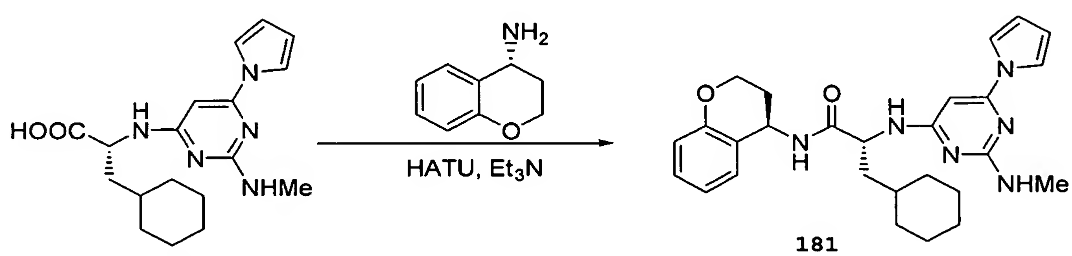


According to Scheme 22, a solution of t-butyl ester of D-cyclohexylalanine (2.7 g, 11.87 mmol), 2,4-dichloro-6-(1-pyrrolyl)pyrimidine (2.54 g, 11.87 mmol) and diisopropylethylamine (1.53 g, 11.87 mmol) in DMF was heated to 90 °C for 24 h. After aqueous work up the crude product was purified by chromatography (silica, hexane:EtOAc, 9:1). The more polar spot was the desired regioisomer **177**. Yield 600 mg.

A solution of the regioisomer **177** (600 mg, 1.48 mmol) in 10 mL of *n*-butanol containing 4 mL of cyclopropylamine was heated to 90 °C in a sealed tube overnight. The solvent was removed and the product **178** was purified by chromatography (silica, hexane:EtOAc, 9:1). Yield 486mg. $(M+H)^+$: 426.3

A solution of the *t*-butylester **178** (486 mg, 1.14 mmol) in 10 mL of 1:1 DCM:TFA was stirred overnight. The solvent was removed and the residue was taken in EtOAc . The EtOAc layer was washed several times with water and the solvent was removed *in vacuo* to provide 367 mg of the carboxylic acid. $(M+H)^+$: 370.8

4-Aminomethylpyridine N-oxide dihydrochloride (200mg, 1.01 mmol) was suspended in 3 mL of dry DMF and 200 mg of Et_3N (1.98 mmol) was added. The contents were stirred for 15 min. In the mean time, a solution of the carboxylic acid (100 mg, 0.27 mmol) from the previous step and Et_3N (300 mg, 2.97 mmol) in 5 mL of DMF was cooled in a ice bath and HATU (100 mg, 0.26 mmol) was added. After stirring for 3 min, aforementioned solution of 4-aminomethylpyridine N-oxide was added and the stirring was continued for 3 days. Aqueous work up and chromatography (silica, EtOAc:MeOH, 85:15) gave 19 mg of **179**. (M+H)+: 476.6.

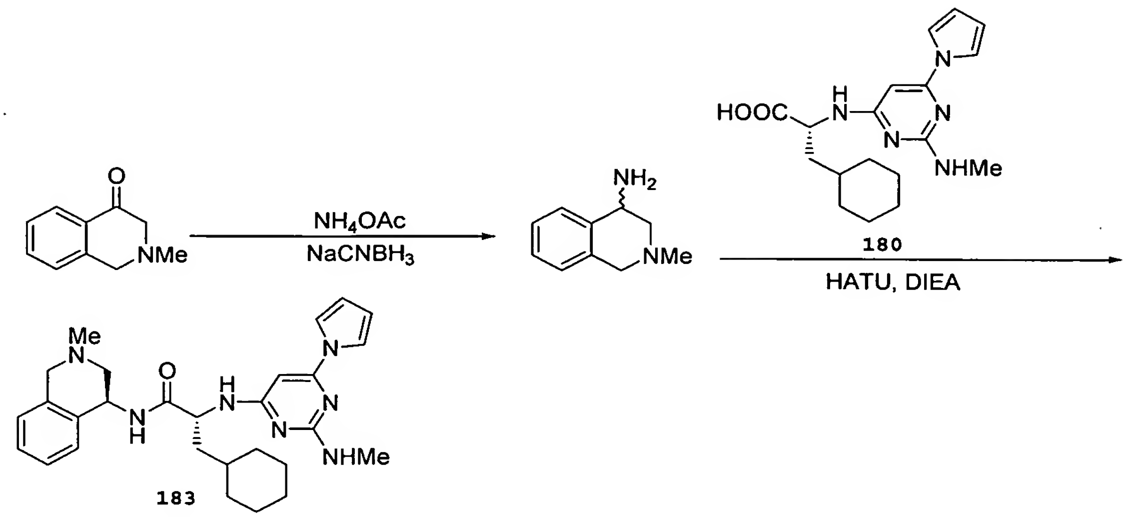


180

A solution of the carboxylic acid **180** (197 mg, 0.57mmol), HATU (218 mg, 0.57 mmol) and Et_3N (172 mg, 1.70 mmol) in 5 mL of dry DMF was stirred for 5 minutes. Then a solution of (*R*)-4-aminochroman (81 mg, 0.54 mmol) in 2 mL of dry DMF was added and the contents were stirred overnight. After aqueous work up, the residue was purified by chromatography (silica, hexane:EtOAc, 1:1) to

provide 32 mg of **181**. $(M+H)^+$: 475.2.

Scheme 23

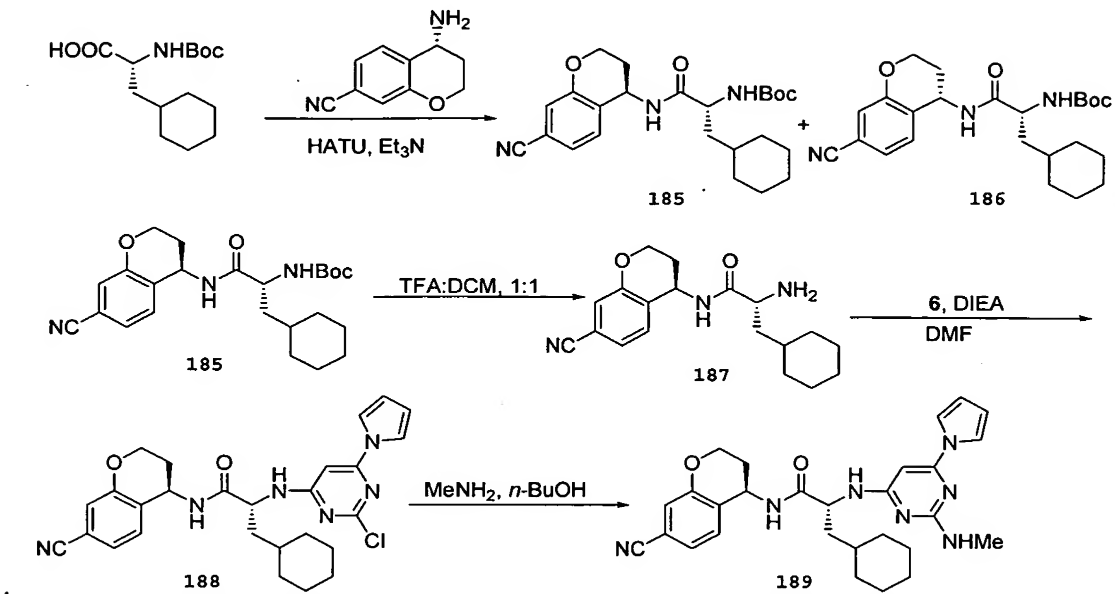


According to Scheme 23, a mixture of 2-methyl-2,3-dihydro-4-(*1H*)-isoquinolone (630 mg, 3.9 mmol, Nichols, D. E. et al.; WO9706799), ammonium acetate (3.0 g, 39 mmol) and $NaCNBH_3$ (491 mg, 7.8 mmol) in 25 mL of dry methanol was stirred for 2 days at RT. The solvent was removed and the residue was acidified to pH 2 to destroy the excess $NaCNBH_3$. After basification with aq Na_2CO_3 to pH 10, the product was extracted into ether. The ether layer was dried (K_2CO_3) and the solvent was evaporated to provide 330 mg of the racemic 4-amino-2-methyltetrahydroisoquinoline. ^1H NMR ($CDCl_3$): δ 2.20 (bs, 2H, NH_2), δ 2.60 (s, 3H, NCH_3), δ 2.90 (d, 2H, CHCH_2N), δ 3.55 (d, 1H, ArCH_2N), δ 3.90 (d, 1H, ArCH_2N), δ 4.15 (t, 1H, Ar*CH*N), δ 7.20-7.60 (m, 4H, ArH).

4-Amino-2-methyltetrahydroisoquinoline (320 mg, 1.97 mmol) was coupled with *N*-(2-methylamino-4-(1-pyrrolyl)-6-pyrimidinyl)-D-cyclohexylalanine (**180**) (237 mg, 0.69 mmol) using HATU as described earlier. After aqueous work up, the residue was purified by chromatography (silica, EtOAc). The diastereomer **183** with higher R_f was assigned *R*-stereochemistry at the benzylic center based on its biological activity, yield: 78 mg, $(M+H)^+$: 488.2. The more polar isomer was

assigned *S*-stereochemistry, yield: 71 mg, $(M+H)^+$: 488.1

Scheme 24

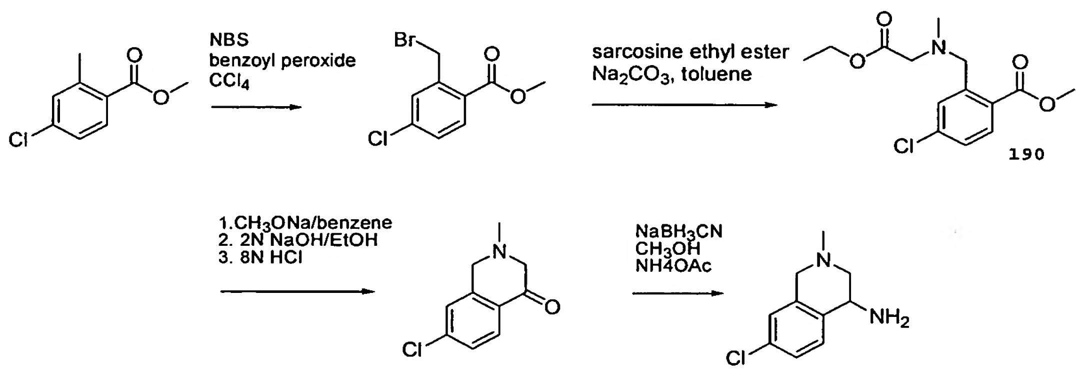


According to Scheme 24, HATU (1.165 g, 3.07 mmol) was added at 0 °C to a solution of *N*-Boc-D-cyclohexylalanine (831 mg, 3.07 mmol) and Et_3N (620 mg, 6.14 mmol) in 15 mL of dry DMF. After stirring for 2 min , 7-cyano-4-chromanylamine (540 mg, 3.068 mmol) was added and the stirring was continued overnight. After aqueous work up and chromatography (silica, hexane:EtOAc, 70:30), 420 mg of the less polar diastereomer **186** $(M+H^+$: 427.8), and 380 mg of the more polar diastereomermer **185** $(M+H^+$: 427.8) were obtained. A solution of the more polar diastereomer **185** (380 mg, 0.89 mmol) was stirred in DCM:TFA (1:1) overnight at RT. Aqueous work up at basic pH provided 270 mg of the primary amine **187**.

A mixture of amine **187** (270 mg, 0.82 mmol), DIEA (106 mg, 0.82 mmol) and 2,4-dichloro-6-(1-pyrrolyl)pyrimidine (175 mg, 0.82 mmol) in DMF was heated to 90 °C overnight. Aqueous work up and chromatography (silica, hexane:EtOAc, 1:1) provided 120 mg of the less polar regioisomer and 96 mg of the more polar desired regioisomer **188**.

A solution of the more polar regioisomer **188** (58 mg, 0.11 mmol) in *n*-butanol was saturated with methylamine at –20 °C. The solution was then heated to 90 °C in a sealed tube overnight. After cooling, the solvent was removed *in vacuo* and the residue was purified by chromatography (silica, hexane:EtOAc, 1:1) to provide 25 mg of **189**. $(M+H)^+$: 500.3.

Scheme 25



4-Amino-7-chloro-2-methyltetrahydroisoquinoline was prepared as shown above in Scheme 25: To a stirred solution of methyl 4-chloro-2-methylbenzoate (8.9g, 48.2 mmol) in dry carbon tetrachloride (150ml) were added N-bromosuccinimide (9.4g, 53.0 mmol) and a catalytic amount of benzoyl peroxide. The reaction was refluxed under stirring for 12 h and then filtered. Removed solvent from filtrate in vacuo to give 12.0g of the crude benzyl bromide. NMR (deuteriochloroform): δ 3.92 (s, 3H, CH_3), 4.92 (s, 2H, CH_2), 7.34 (d, 1H, ArH), 7.46 (s, 1H, ArH), 7.79 (d, 1H, ArH).

To a mixture of sarcosine ethyl ester hydrochloride (7.4g, 63 mmol), sodium carbonate (8.2g, 77.4 mmol), and toluene (300ml) was added a solution of the benzyl bromide (12.0 g, 45.5 mmol) in toluene at room temperature. The reaction was heated at 85 ºC with stirring for 12 h, cooled to room temperature, and then filtered. The filtrate was collected and extracted with 3N HCl (150 ml x 3). The aqueous layer was collected, basified with saturated Na_2CO_3 solution, and extracted with ether (150 ml x 3). To remove the solvent from the organic solution give 8.4g (61%) of **190**. NMR ($CDCl_3$): δ 1.30 (m, 3H, CH_3), 2.38 (s, 3H, CH_3),

3.3 (s, 2H, CH_2), 3.86 (s, 3H, CH_3), 4.0 (S, 2H, CH_2), 4.18 (m, 2H, CH_2), 7.26 (D, 1H, ArH), 7.60 (s, 1H, ArH), 7.74 (D, 1H, ArH).

Freshly cut sodium (0.84 g, 36.3 mmol) was added to absolute methanol (30 ml) under argon. The reaction was refluxed until sodium metal disappeared. A solution of **190** (8.4 g, 27.9 mmol) in dry toluene (150 ml) was added slowly. The mixture was heated at reflux to remove extra methanol via a Dean Stark trap. Fresh dry toluene (150 ml) was added and refluxed for 2h. After cooling, solvent was removed under vacuum. The remains dissolved in ethanol (150 ml) were treated with 2N NaOH (250 ml). It was refluxed for 1.5h, cooled to room temperature, acidified with 8N HCl, and then refluxed for 2.5 h. The reaction mixture was cooled to room temperature, basified with 6N NaOH, extracted with methylene chloride (150 ml x 3). The organic layer was dried over Na_2SO_4. The solvent was removed in vacuo. The residue was purified by chromatography with EtOAc/Hexane (1:1) to give 1.82g (31%) of the isoquinolone. NMR ($CDCl_3$): δ 2.46 (s, 3H, CH_3), 3.3 (s, 2H, CH_2), 3.7 (s, 2H, CH_2), 7.22 (d, 1H, ArH), 7.3 (s, 1H, ArH), 7.96 (d, 1H, ArH).

To a mixture of compound tetrahydroisoquinolone (1.8 g, 9.3 mmol) and NH_4OAc (7.1 g, 9.3 mmol) in dry methanol (80 ml) was added $NaCNBH_3$ (2.9 g, 46.4 mmol). The reaction was stirred at room temperature for 3 days. Removed solvent under vacuum. The residue was separated by silica gel chromatography column with methanol/ammonia hydroxide/ethyl acetate (20:1:79) to give 1.1g (60%) of 4-Amino-7-chloro-2-methyltetrahydroisoquinoline. NMR ($CDCl_3$): δ 1.7 (2H, CH_2), 2.4 (3H, CH_3), 2.66 (2H, CH_2), 7.0(1H, ArH), 7.2 (1H, ArH), 7.28 (1H, ArH).

All of the compounds shown in the tables below have been examined by high resolution mass spectrometry and have provided MH^+ ions and fragments consistent with the structures shown.

Bioassays

Tissues are taken from New Zealand white rabbits (1.5-2.5 kg) and Duncan Hartley guinea pigs (250-350g) of either sex, killed by stunning and exsanguination. Human umbilical cords are obtained after spontaneous delivery at term. The rabbit jugular vein (RbJV) and the guinea pig ileum (GPI), are two preparations containing B_2 receptors. The rabbit aorta (RbA) contains B_1 receptors, and the human umbilical vein (HUV) is a mixed preparation containing both B_1 and B_2 receptors. Helical strips of RbJV, treated with 1 μmol/L of captopril to avoid peptide degradation, are prepared according to Gaudreau et al. [Can. J. Physical, Pharmacol. 59, 371-379 (1981)] Helical strips of RbA devoid of endothelium are prepared according to Furchgott and Bhadrakom. [J. Pharacol. Exp. Ther. 108, 124-143 (1953)] Longitudinal segments of GPI are prepared with the procedure described by Rang [Brit. J. Pharmacol. 22, 356-365 (1964)]]. Helical strips of HUV are prepared according to Gobeil et al. [Brit. J. Pharmacol. 118, 289-294 (1996)]. Unless otherwise indicated below, the tissues are suspended in 10-mL organ baths containing warm (37°C), oxygenated (95% O_2- 5% $C0_2$) Krebs solution of the following composition in mmol/L; NaCl: 118. 1; KCl: 4.7; $CaC1_26H_20$: 2.5; KH_2PO_4: 1.2; $MgSO_47H_20$:1.18; $NAHCO_3$: 25.0 and D-Glucose: 5.5. The RbA are stretched with an initial tension of 2 g, whereas the RbJV and the GPI are loaded with 0.5 g. Changes of tension produced by the various agents are measured with Grass isometric transducers (model FT 03C, Grass Instrument Co., Quincy, Mass.). Myotropic contractions are displayed on a polygraph. Before testing the drugs, the tissues are allowed to equilibrate for 60-120 minutes, during which time the tissues are repeatedly washed and the tension readjusted every 15 min.

At the beginning of each experiment, a submaximal dose of bradykinin (BK) (9 nmol/L), is applied repeatedly on the RbJV, the GPI or the HUV to ensure that tissues responded with stable contractions. In the RbA, the B_1 preparation whose response has been shown to increase during the incubation *in vitro*, desArg^9 K (550 nmol/L) are applied 1,3 and 6 h after the equilibration period, in order to

monitor the progressive increase of sensitivity of the tissue which generally reaches the maximum after 3-6 h.

Repeated applications of a single and double concentration of BK (on RbJV, GPI and HUV) and of desArg^{9}BK (RbA and HUV) are made in the absence and in presence of the test compounds to evaluate their apparent affinities as antagonists, in terms of pA_2 ($-\log_{10}$ of the molar concentration of antagonist that reduces the effect of a double concentration of agonist to that of a single one). The antagonists are applied 10 min before measuring the myotropic effects of either BK (the B_2 receptor agonist) or desArg^{9}BK (the B_1 receptor agonist). Pharmacological assays on the HUV (a mixed B_1 and B_2 receptor preparation) are done in presence of either HOE140 (400 nmol/L) (a potent B_2 receptor antagonist) or Lys[Leu^8]des Arg^{9}BK (1 μmol/L) (a potent B_1 receptor antagonist) (applied 10 min prior to the tested agents) to study the B_1 and the B_2 receptors, respectively. All kinin antagonists are initially applied to tissues at concentration of 10 μg/mL to measure their potential agonistic activities (α^E) in comparison with BK (in the B_2 receptor preparations) or desArg^{9}BK (in the B_1 receptor preparations). The compounds of the present invention exhibit inhibition at very low concentrations only when tested in human or primate systems; thus the foregoing (and following) tests in rabbit and rodent tissues are useful only for demonstrating lack of undesired effects on other receptors than B_1 and in other tissues than human. In order to determine the potency of compounds of the invention, those tests that employ rabbit and rodent tissues are modified to employ human and primate tissues, as well known to persons in the art.

Streptozotocin has been extensively used to produce type I diabetes in animals. This experimental disease is characterized by a mild inflammatory reaction in the Langerhans islets. Male C57L/K_3 mdb mice are injected with streptozotocin (40mg/kg) for 5 consecutive days. The kinin B_1 receptor antagonists are injected subcutaneously to STZ mice at 300 μg/Kg bw twice a day and 500 μg/Kg per day, respectively. Treatment with antagonists is started 3 days after STZ

and lasts for 10 days. Plasma glucose is determined by the glucose oxidase method, and urinary samples are assayed at 13 days for proteins, nitrites and kallikreins. Diabetic mice show hyperglycemia and increased diuresis, marked proteinuria and increased excretion of nitrites and kallikreins. B_2 receptor antagonists reduce water and protein excretion, compared to STZ group; STZ mice treated with B_1 receptor antagonists show normal glycemia and normalization of diuresis, protein, nitrite and kallikrein excretion.

The contractile response of the portal vein (a suitable preparation for B_1-BK studies) obtained from untreated 8-week old spontaneously hypertensive rats (SHR), is exaggerated and susceptible to enhanced capillary hydrostatic pressure and plasma leakage. Desendothelialized portal vein segments obtained from SHR are mounted in organ baths containing a Krebs solution for isometric contraction studies (baseline tension: 0.5 g). Test compounds are administered on portal vein segments obtained from normal rats and SHR, to establish dose-response curves.

Bradykinin B_1 receptor binding in human tissue is determined by the method of Levesque *et al*. [Immunopharmacology 29, 141-147 (1995); and Immunopharmacology 28, 1-7 (1994)]. Human embryonic fibroblast cells from the IMR-90 line (available from ATCC as CCL 186) are grown in minimal essential medium as described by Menke et al [J.Biol.Chem. 269, 21583-21586 (1994)]. After 24 hours, the culture medium is replaced with low serum media (0.4% fetal bovine serum) containing recombinant human IL-1β (0.25 mg/mL) and the cells are further incubated for 4-5 hours. The cells are harvested with trypsin and resuspended in Medium 11995-065 (Gibco, Gaithersburg, MD, USA) supplemented with L-glutamine, non-essential amino acids and 10% fetal bovine serum at 1.7×10^6 cells/mL. Thirty microliters of the cell suspension in a plate is mixed with 10 μL of straight buffer [1 L of Medium 199 (Gibco, Gaithersburg, MD, USA), 25 mL of HEPES buffer, 1 g bovine serum albumin 3μM amastatin, 1μM captopril and 1μM phosphoramidon (Sigma, St. Louis, MO, USA)] or 10 μL of buffer containing 5 to 50 μM B_1-BK antagonist and 10 μL of 11 μM ^{3}H-

desArg^{10}-kallidin. The plates are incubated at room temperature for about 1.5 hours. After incubation, each well is washed with 150 μL of ice-cold PBS at pH 2.4. The contents are transferred to a glass fiber plate that has been pretreated with polyethyleneimine and the plate is air dried. Scintillation fluid is added and the resulting solution is counted in a gamma counter for 10 minutes. Statistical analysis is performed on the saturation curves. Scatchard regression parameters are calculated from the mean saturation data using a computer program (Tallarida and Murray, 1987). The resulting B_{max} and K_d values and their respective SEM are compared in order to assess statistical differences using Student's *t*-test. The compounds of the invention exhibit Ki's below 10μM. Specific examples of compounds which have been synthesized and tested are shown in ~~Table~~ Tables 1 and 2. Those compounds in Table 1 exhibited K_i's of 1 to 500 nM; those in Table 2 exhibited K_i's of 501 nM to 10μM.

Potency and efficacy in human tissue are assessed as follows: Human umbilical cords are obtained within 24 hours following normal deliveries and are stored in physiological salt solution (PSS) at 4° C. The composition of the PSS is as follows: 118mM NaCl, 4.6 mM KCl, 1.2 mM KH_2PO_4, 1.2 mM $MgSO_4$, 2.5mM $CaCl_2$, 0.026 mM $CaNa_2EDTA$, 10 mM glucose, and 24.8 mM $NaHCO_3$. The umbilical vein is carefully dissected and placed in ice-cold, PSS, which is continuously aerated with 95% 0_2/5%CO_2 to maintain pH at 7.4. Excess connective tissue is removed, and rings 2-3 mm in length are prepared. The rings are mounted between stainless steel wires in water-jacketed tissue baths for measuring contractile function. The rings are attached to a force-displacement transducer for measuring tension development. The baths contain 15 mL of oxygenated PSS maintained at 37° C.

After mounting, resting tension is adjusted to 1.0 g and the rings are equilibrated for 60 minutes before beginning the experiment. The tissue baths are rinsed with fresh PSS 30 min and 60 min after mounting the rings. Following each rinse, the resting tension is adjusted to 1.0 g. After the equilibration period, the

rings are depolarized by adding increasing concentrations of KCl to the tissue bath until a maximum increase in tension is obtained. The bath is rinsed with fresh PSS, and the resting tension readjusted to 1.0 g. the response to KCl is repeated two additional times at 30-min intervals. The maximum increases in tension obtained following the second and third assessments of the response to KCl are averaged. The value is used to normalize the direct response to the test compound, and also the response to a reference bradykinin receptor agonist.

Evaluating an Antagonist Effect : After assessing the responses to KCl, the test compound is added to the tissue bath. Thirty minutes later, the following concentrations of desArg^{10} Kallidin are added to the tissue bath: 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30, 100 nM. The response to each concentration of desArg^{10} Kallidin is normalized as a percentage of the maximum constrictor response to KCl.

Evaluating a Direct Effect: After assessing the responses to KCl, the following concentrations of the test compound are added to the tissue bath: 1, 3, 10, 30, 100, 300, 1000, 3000 and 10000 nM. Alternatively, an equivalent volume of the vehicle used to solubilize the test compound is added to the tissue baths. Each new concentration is added to the bath after the response to the previous concentration has reached equilibrium. If no response is obtained, the next concentration of test compound is added to the bath 15 min after the previous concentration.

While it may be possible for the compounds of formula (I) to be administered as the raw chemical, it is preferable to present them as a pharmaceutical composition. According to a further aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically carriers thereof and optionally one or more other therapeutic ingredients, as discussed below. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), rectal and topical (including dermal, buccal, sublingual and intraocular) administration. The most suitable route may depend upon the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a compound of the invention or a pharmaceutically acceptable salt or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Pharmaceutical formulations, particularly topical formulations, may additionally comprise steroidal anti-inflammatory drugs, which may include but are not limited to alclometasone dipropionate, amcinonide, beclamethasone dipropionate, betamethasone benzoate, betamethasone dipropionate, betamethasone valerate, budesonide, clobetasol propionate, clobetasone butyrate, desonide, desoxymethasone, diflorasone diacetate, diflucortolone valerate, flumethasone pivalate, fluclorolone acetonide, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone preparations, fluprednidene acetate, flurandrenolone, halcinonide, hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone acetate, mometasone furoate and triamcinolone acetonide.

Pharmaceutical formulations may also additionally comprise steroidal anti-inflammatory drugs for oral administration. These may include but are not limited to finasteride, betamethasone and hydrocortisone.

Alternatively or additionally, pharmaceutical formulations may additionally comprise nonsteroidal anti-inflammatory drugs (NSAIDS), which may include but are not limited to aminoarylcarboxylic acids (fenamic acid NSAIDs), arylacetic

acids, arylbutyric acids such as fenbufen, arylpropionic acids (profens), pyrazoles such as epirizole, pyrazolones such as phenylbutazone, salicylic acids such as aspirin, oxicams and other compound classes that may be considered as NSAIDS including leucotriene antagonists. These formulations exhibit both the additive effects of the individual components and synergistic effects from blocking of multiple pathways in the pain and inflammation pathway.

Propionic acid NSAIDs are non-narcotic analgesics/nonsteroidal antiinflammatory drugs having a free $-CH(CH_3)COOH$ group, which optionally can be in the form of a pharmaceutically acceptable salt group, e.g., $-CH(CH_3)COO^- Na^+$. The propionic acid side chain is typically attached directly or via a carbonyl function to a ring system, preferably to an aromatic ring system. Exemplary propionic acid NSAIDS include: ibuprofen, indoprofen, ketoprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, pirprofen, carpofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofen, fluprofen, and bucloxic acid. Structurally related propionic acid derivatives having similar analgesic and antiinflammatory properties are also intended to be included in this group. Profens, as well as NSAIDs from other classes, may exhibit optical isomerism. The invention contemplates the use of pure enantiomers and mixtures of enantiomers, including racemic mixtures, although the use of the substantially optically pure eutomer will generally be preferred.

Acetic acid NSAIDs are non-narcotic analgesics/nonsteroidal antiinflammatory drugs having a free $-CH_2COOH$ group (which optionally can be in the form of a pharmaceutically acceptable salt group, e.g. $-CH_2COO^-Na^+$, typically attached directly to a ring system, preferably to an aromatic or heteroaromatic ring system. Exemplary acetic acid NSAIDS include: ketorolac, indomethacin, sulindac, tolmetin, zomepirac, diclofenac, fenclofenac, alclofenac, ibufenac, isoxepac, furofenac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, and fenclozic acid. Structurally related acetic acid derivatives having similar analgesic and antiinflammatory properties are also intended to be

encompassed by this group.

Fenamic acid NSAIDs are non-narcotic analgesics/nonsteroidal antiinflammatory drugs having a substituted N-phenylanthranilic acid structure. Exemplary fenamic acid derivatives include mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, and tolfenamic acid.

Biphenylcarboxylic acid NSAIDs are non-narcotic analgesics/nonsteroidal antiinflammatory drugs incorporating the basic structure of a biphenylcarboxylic acid. Exemplary biphenyl-carboxylic acid NSAIDs include diflunisal and flufenisal.

Oxicam NSAIDs are N-aryl derivatives of 4-hydroxyl-1,2-benzothiazine 1,1-dioxide-3-carboxamide. Exemplary oxicam NSAIDs are piroxicam, tenoxicam sudoxicam and isoxicam.

Pharmaceutical formulations may also include cyclo-oxygenase (COX) inhibitors (including arylpropionic acids such as ibuprofen and salicylic acids such as aspirin), selective cyclooxygenase-1 (COX-1) inhibitors or selective cyclo-oxygenase-2 (COX-2) inhibitors such as rofecoxib or celecoxib. These formulations also exhibit both the additive effects of the individual components and synergistic effects from blocking of multiple pathways in the pain and inflammation pathway.

The term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic acids and bases and organic acids and bases. When the compounds of the present invention are basic, salts may be prepared from pharmaceutically acceptable non-toxic acids including inorganic and organic acids. Suitable pharmaceutically acceptable acid addition salts for the compounds of the present invention include acetic, benzenesulfonic (besylate), benzoic, camphorsulfonic, citric, ethenesulfonic,

fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric acid, p-toluenesulfonic, and the like. When the compounds contain an acidic side chain, suitable pharmaceutically acceptable base addition salts for the compounds of the present invention include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste. A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide sustained, delayed or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient. Formulations for parenteral administration also include aqueous and non-aqueous sterile suspensions, which may include suspending agents and thickening agents. The formulations may be presented in unit-dose of

multi-dose containers, for example sealed ampules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of a sterile liquid carrier, for example saline, phosphate-buffered saline (PBS) or the like, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol. Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia. It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

Preferred unit dosage formulations are those containing an effective dose, as hereinbelow recited, or an appropriate fraction thereof, of the active ingredient. The compounds of the invention may be administered orally or via injection at a dose from 0.001 to 2500 mg/kg per day. The dose range for adult humans is generally from 0.005 mg to 10 g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the invention which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10mg to 200mg.

The compounds of formula (I) are preferably administered orally or by injection (intravenous or subcutaneous). The precise amount of compound administered to a patient will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors, including the age

and sex of the patient, the precise disorder being treated, and its severity. Also, the route of administration may vary depending on the condition and its severity.

EXAMPLE 1

Aqueous Suspension for Injection

A suspending vehicle is prepared from the following materials:

Polyethylene glycol 4000	30	gm.
Potassium chloride	11.2	gm.
Polysorbate 80	2	gm.
Methylparaben	0.2	gm.
Water for injection q.s.	1000	mL.

The parabens are added to a major portion of the water and are dissolved therein by stirring and heating to 65° C. The resulting solution is cooled to room temperature and the remainder of the ingredients are added and dissolved. The balance of the water to make up the required volume is then added and the solution sterilized by filtration. The sterile vehicle thus prepared is then mixed with 3 gm of B_1- BK inhibitor of the invention (e.g. compound **10**), which has been previously reduced to a particle size less than about 10 microns and sterilized with ethylene oxide gas. This mixture may then be mixed, optionally, with 5 gm of an antiinflammatory (e.g. hydrocortisone), which has been previously reduced to a particle size less than about 10 microns and sterilized with ethylene oxide gas. The mixture is passed through a sterilized colloid mill and filled under aseptic conditions into sterile containers which are then sealed.

EXAMPLE 2

Water-washable cream

The following ingredients are formulated:

Ingredients	Per Cent w/w
Hydrocortisone acetate	0.025
Compound **10**	0.025
Mineral Oil	6.0
Petrolatum	15.0
Polyethylene glycol 1000 monocetyl ether	1.8
Cetostearyl alcohol	7.2
Chlorocresol	0.1
Distilled water to produce 100 parts by weight	

The cortisone and B_1-BK antagonist **10** are ball-milled with a little mineral oil to a particle size of less than 5 microns. The water is heated to boiling, the chlorocresol added and the solution then cooled to 65° C. Then the petrolatum, cetostearyl alcohol and polyethylene glycol ether are mixed together while heating to 65° C. The milled steroid suspension is then added to the melt rinsing the container with mineral oil. The active ingredient oily phase thus prepared is added at 60° C to the chlorocresol aqueous phase at 65° C. The mixture is stirred rapidly while cooling past the gelling point (40° - 45° C.) and the stirring is continued at a speed sufficiently slow to permit the cream to set. The water-washable cream may be used in the treatment of dermatoses using either the open (without occlusion) or occlusive method of drug application.

EXAMPLE 3

Topical Ointment

Hydrocortisone acetate	0.05gm
Compound **10**	1.00gm.
Chloroxine	1.00gm.
Propylene Glycol	7.00gm.
Glyceryl monostearate with emulsifier	5.00gm.
White petrolatum q.s.a.d.	100.00gm.

Heat the propylene glycol to 55° C Add hydrocortisone acetate, compound 10, and chloroxine and mix well. Add the remaining ingredients and mix until melted. Remove from heat and mix slowly until cooled to 45° C, then homogenize.

EXAMPLE 4 - Tablets

Composition per tablet:	
compound **10**	30 mg
Precipitated calcium carbonate	50 mg
Corn Starch	40 mg
Lactose	73.4 mg
Hydroxypropylcellulose	6 mg
Magnesium stearate	(0.05 mL)
Total	200.0 mg

Compound **10**, precipitated calcium carbonate, corn starch, lactose and hydroxypropylcellulose are mixed together, water is added, and the mixture is kneaded, then dried in vacuum at 40°C for 16 hours, ground in a mortar and passed through a 16-mesh sieve to give granules. To this is added magnesium stearate and the resultant mixture is made up into tablets each weighing 200 mg on a rotary tableting machine.

Table 1

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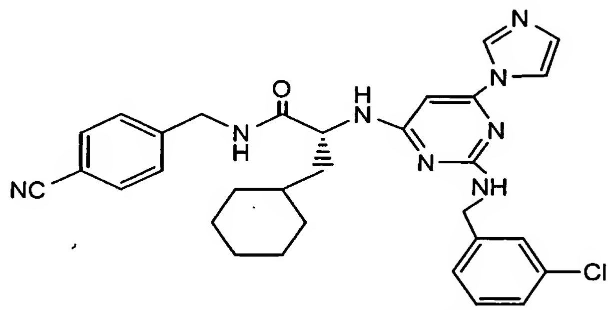
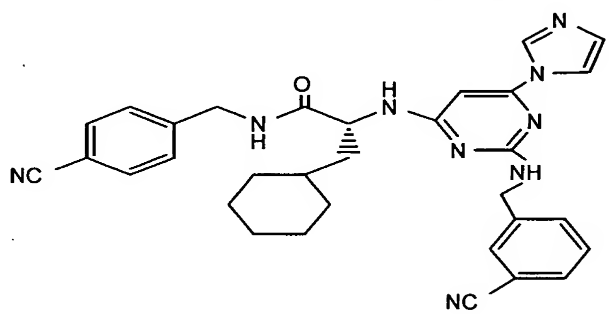
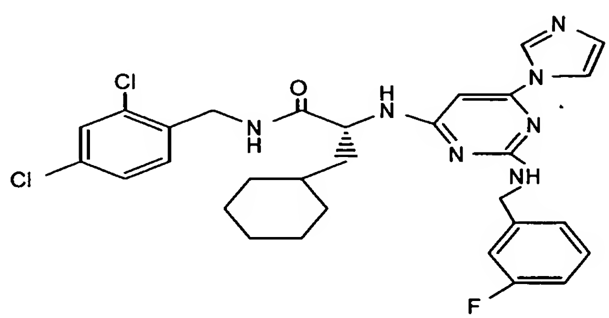
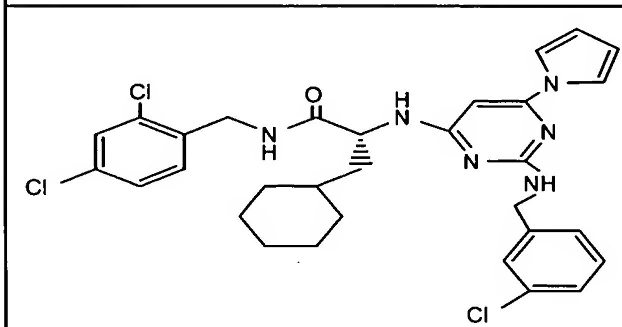
	978163
	645199
	283326
	309799

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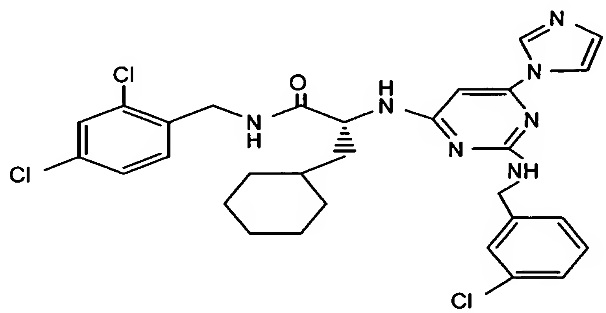
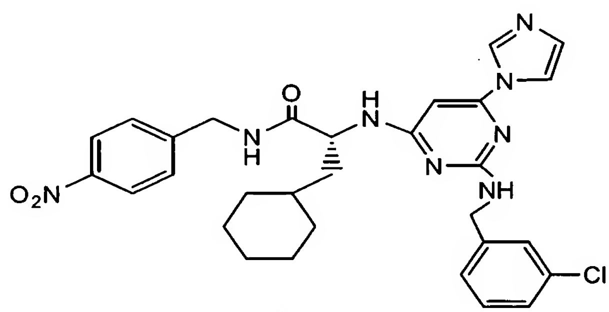
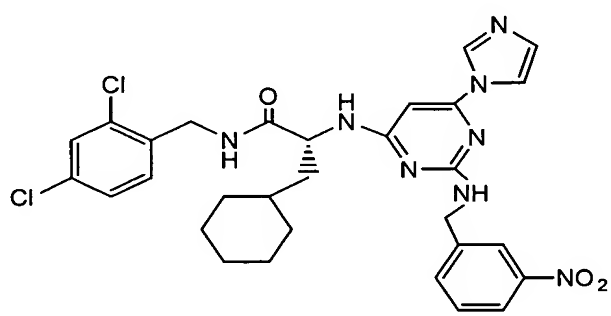
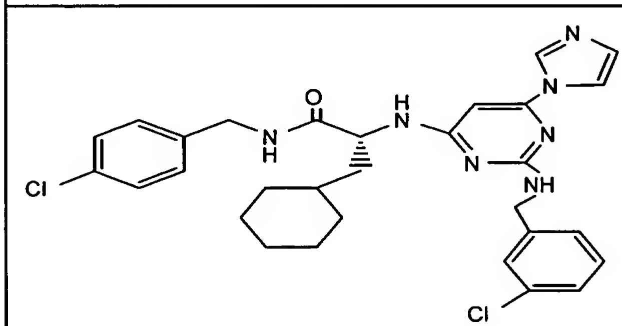
	322835
	697855
	999865
	294578

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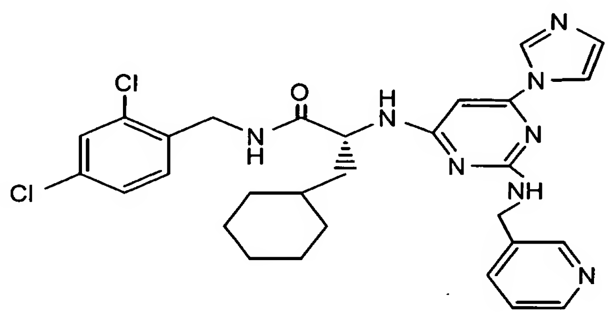
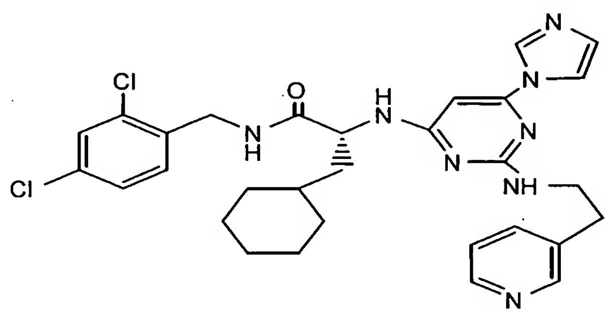
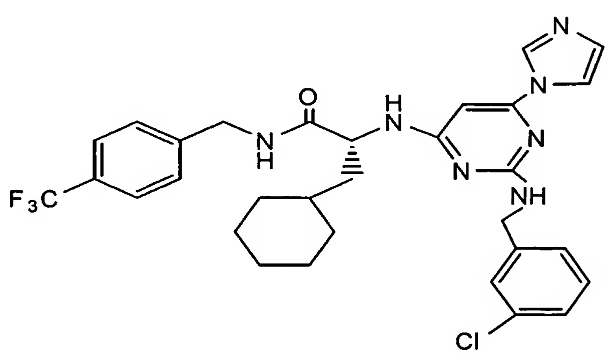
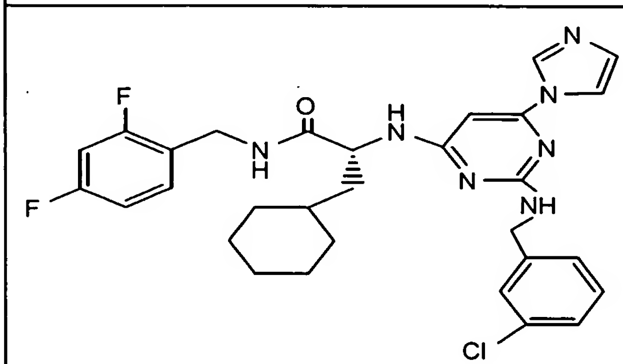
	182337
	214748
	531746
	835218

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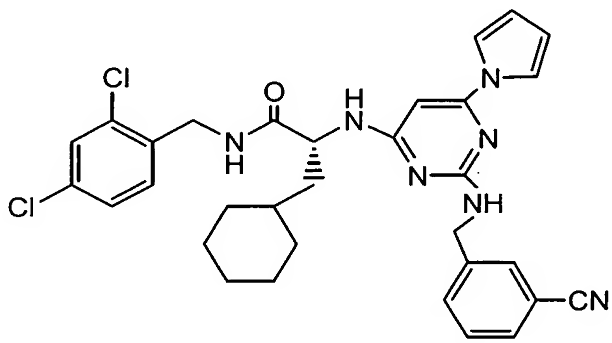
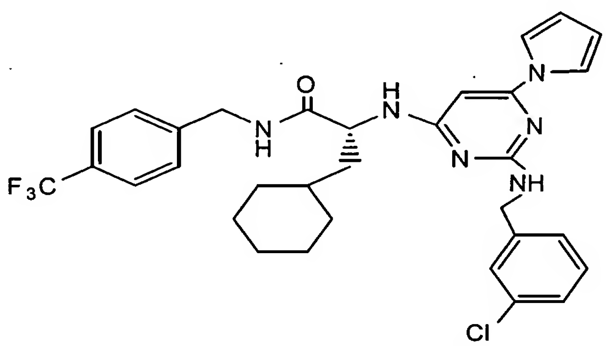
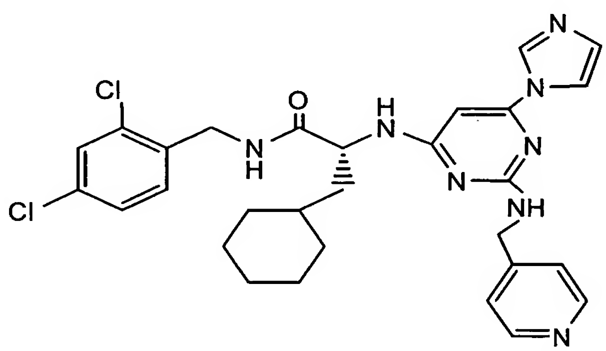
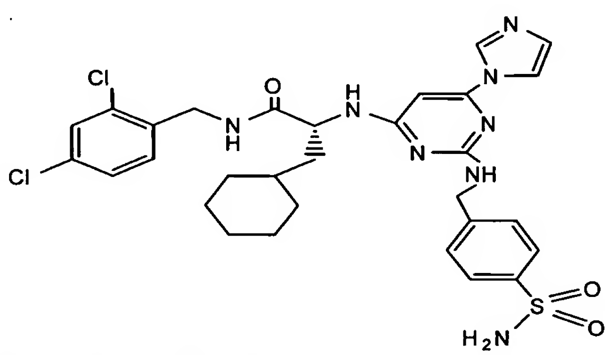
	146684
	020990
	091083
	680690

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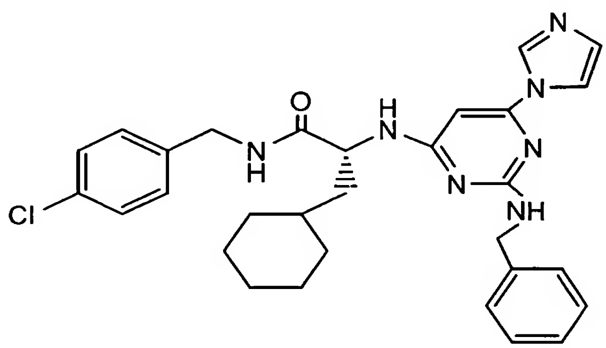
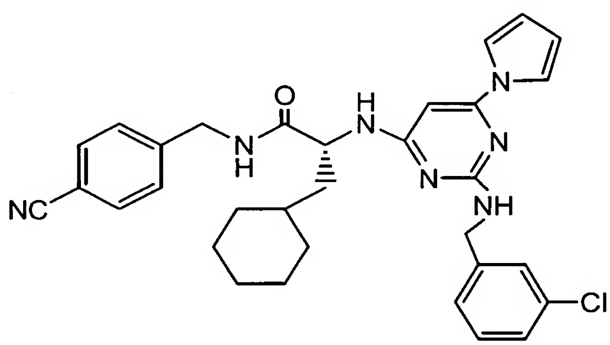
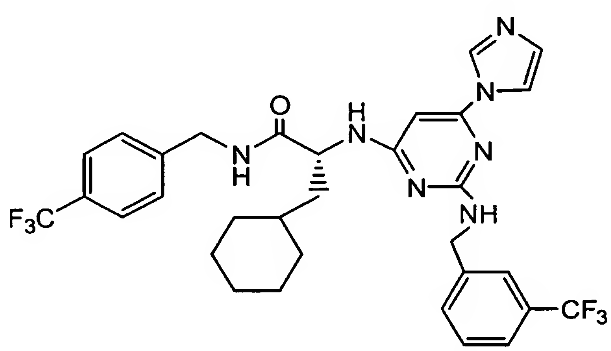
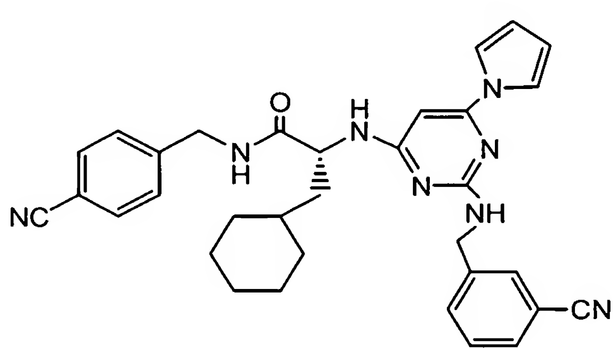
	022238
	292412
	337677
	596668

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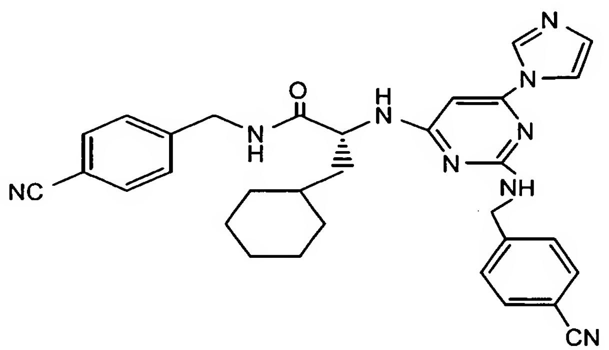
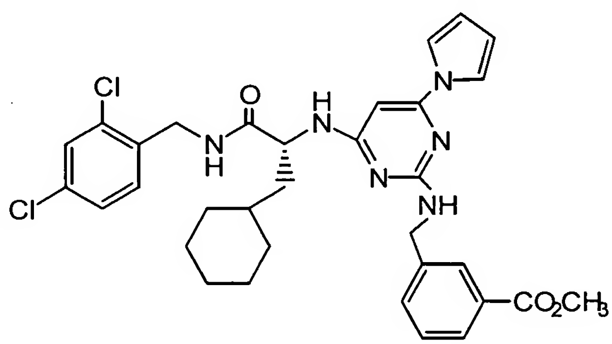
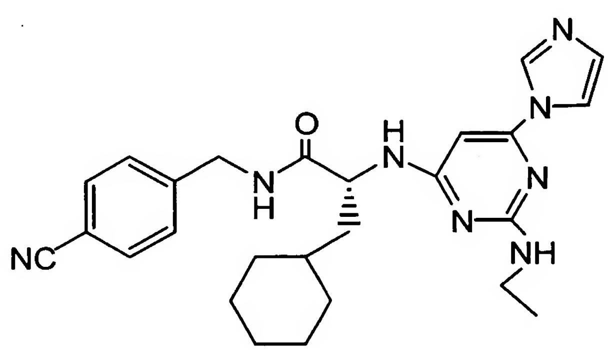
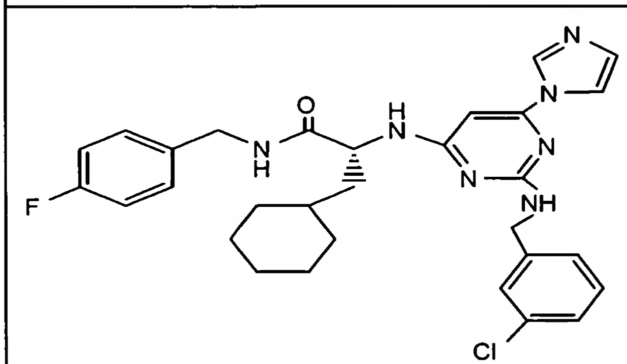
	680800
	919044
	234134
	120005

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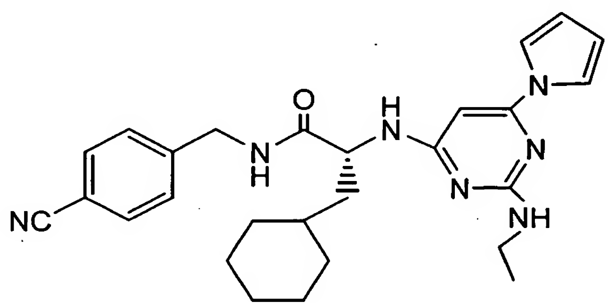
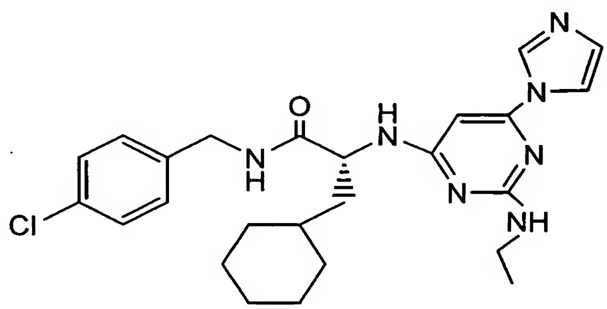
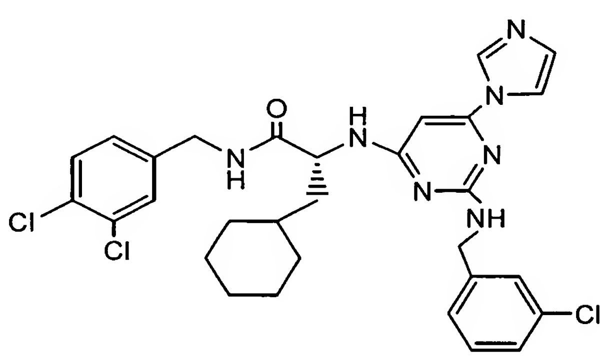
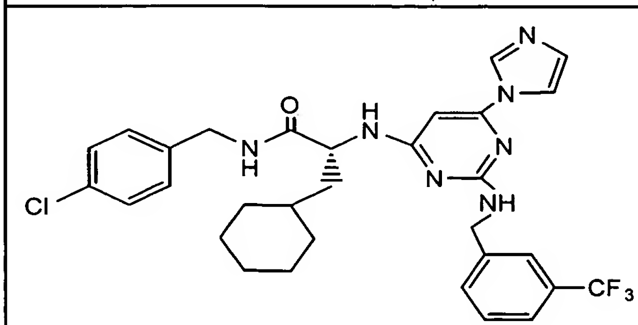
	247664
	115870
	179617
	249564

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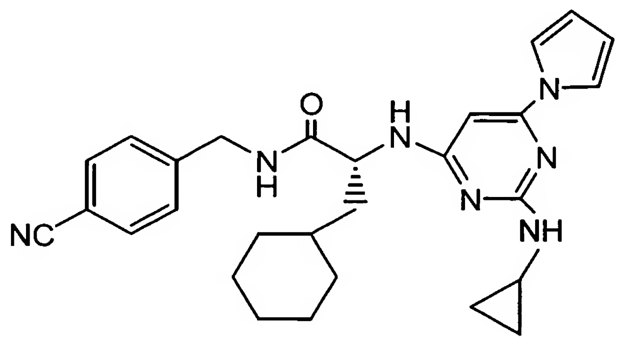
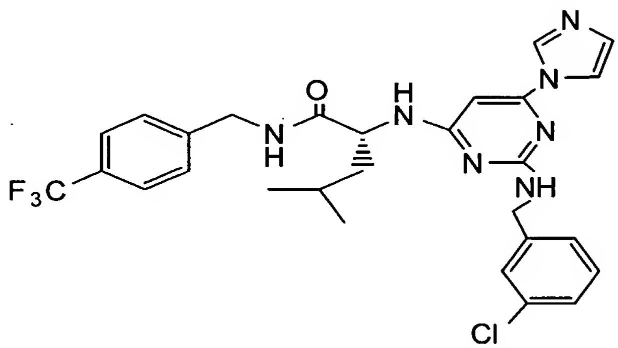
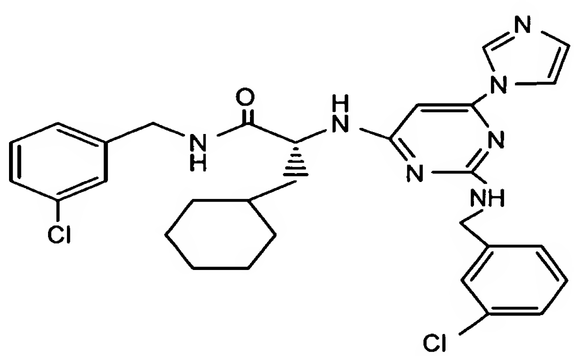
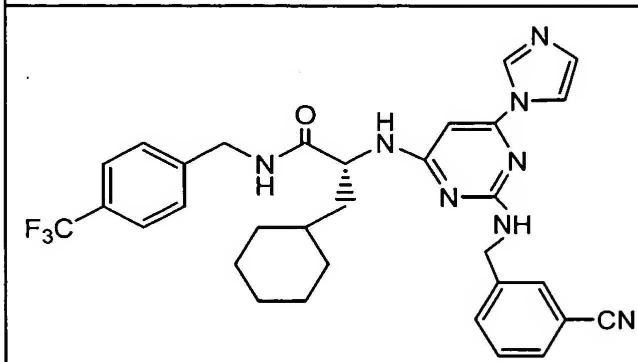
	109900
	240885
	003493
	042066

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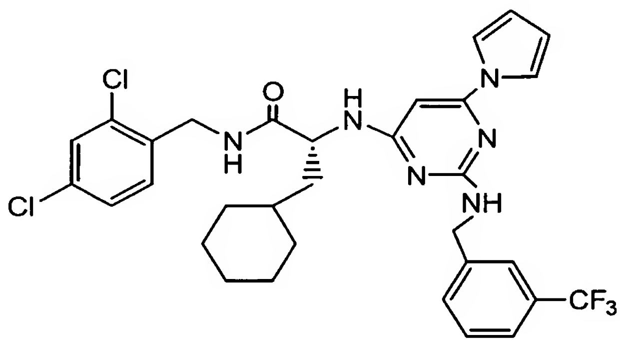
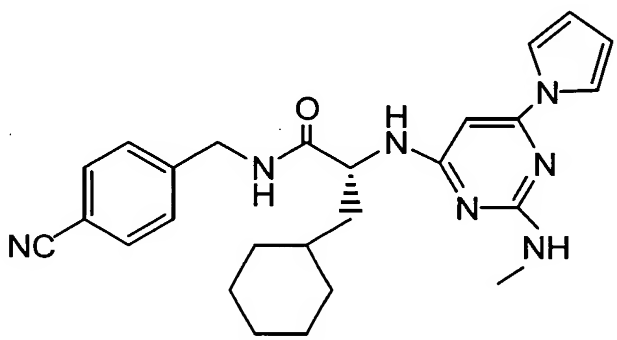
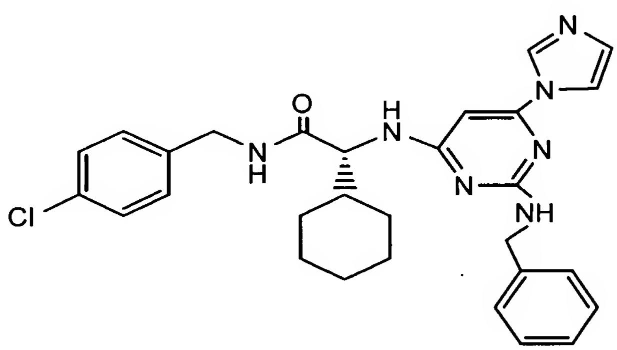
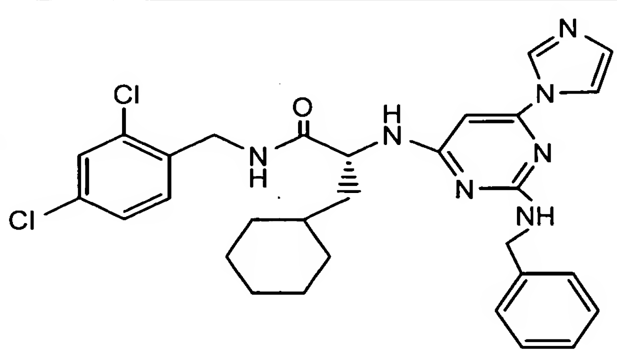
	300801
	730438
	207077
	708899

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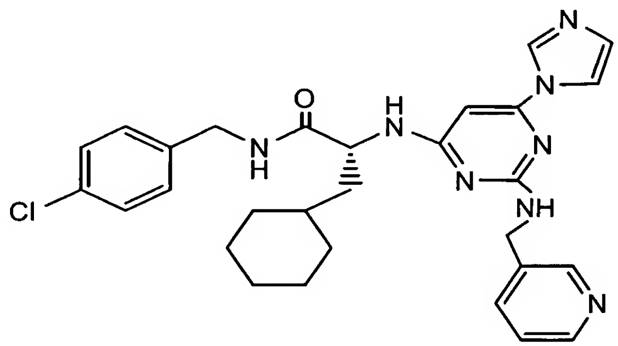
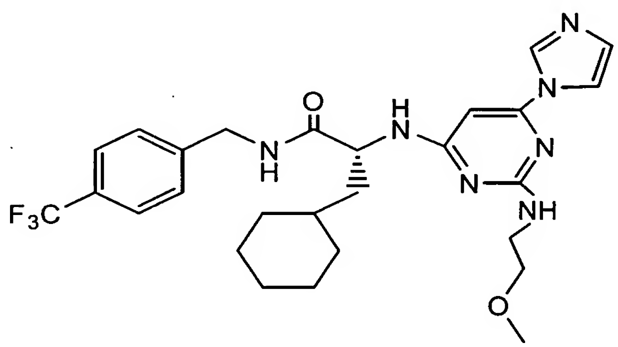
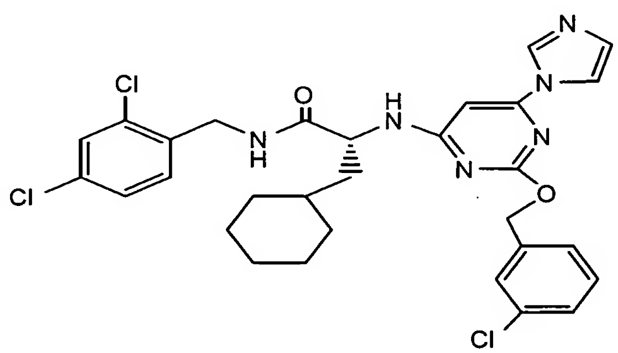
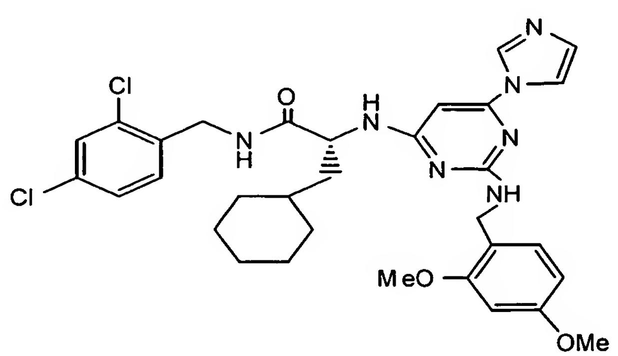
	568105
	422025
	323150
	566861

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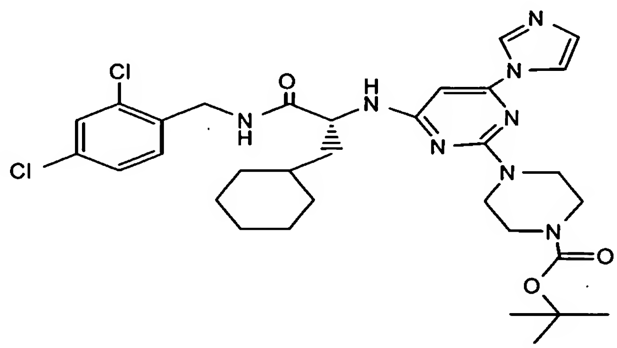
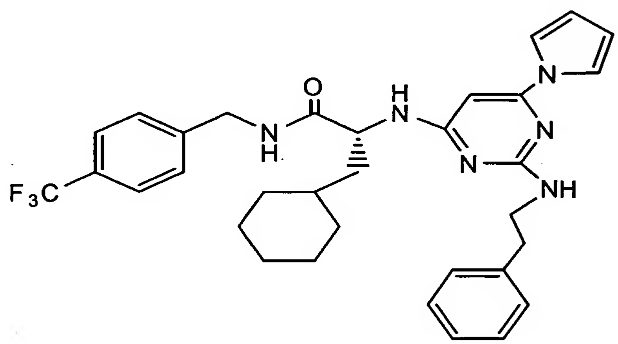
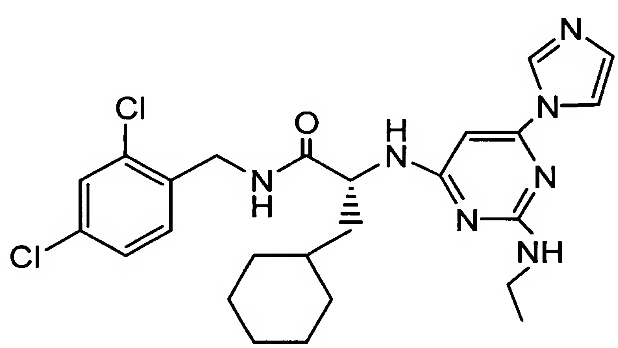
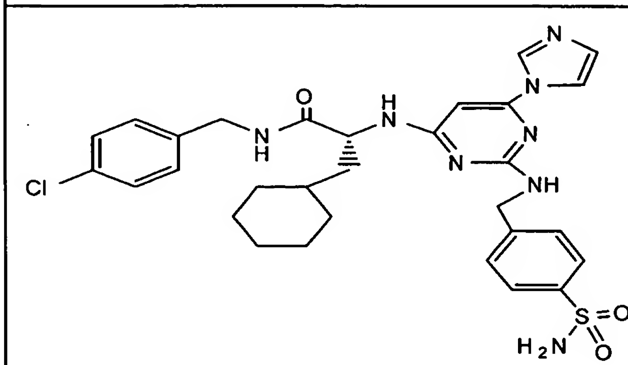
	234930
	048598
	000753
	406301

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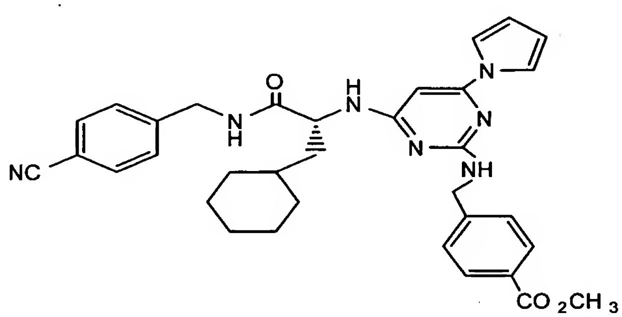
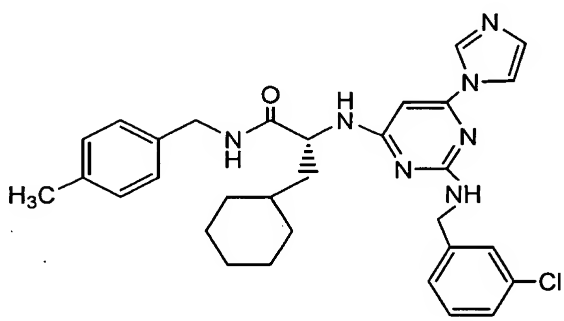
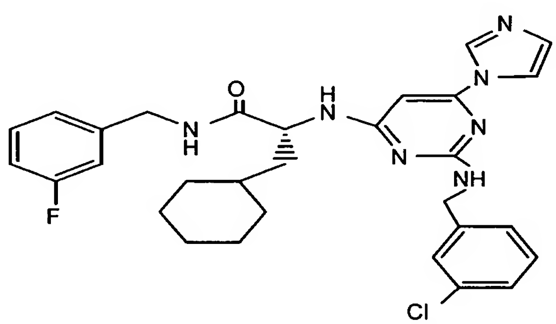
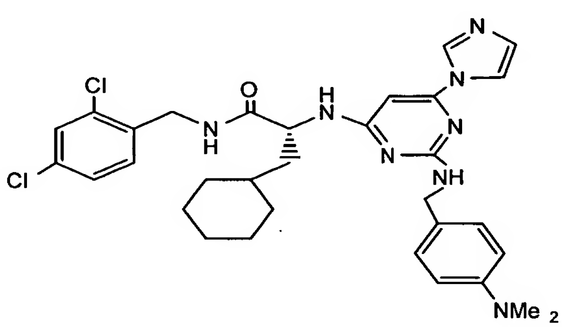
	320650
	189058
	139629
	751675

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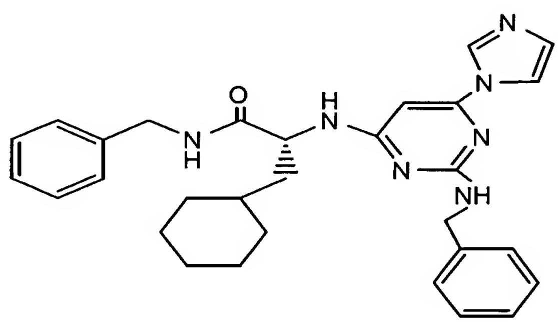
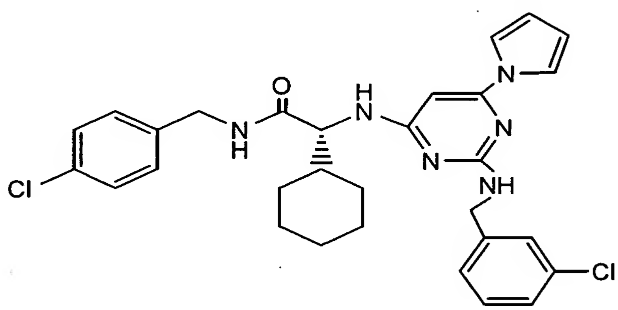
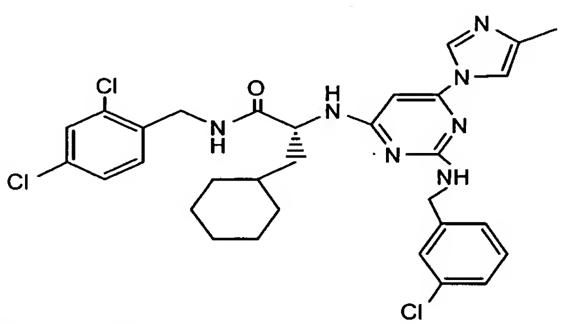
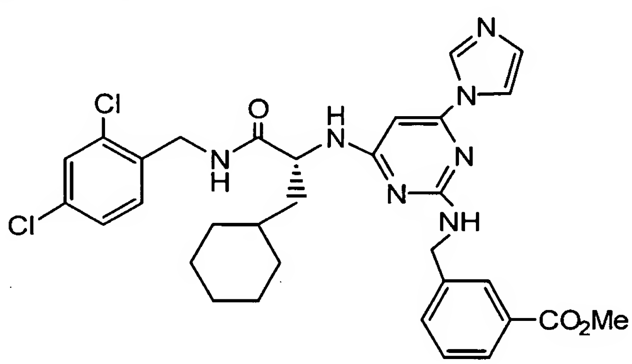
	474275
	172231
	726261
	751597

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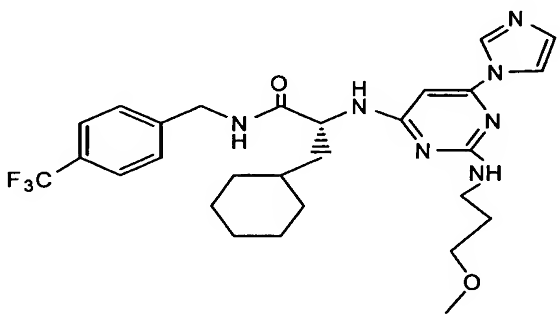
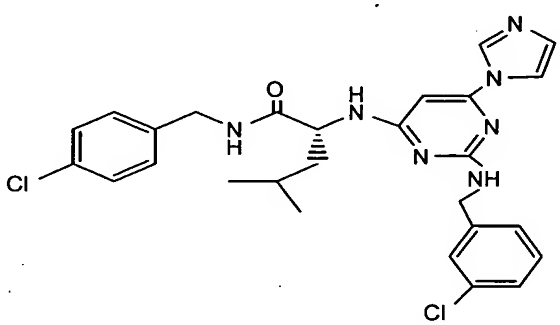
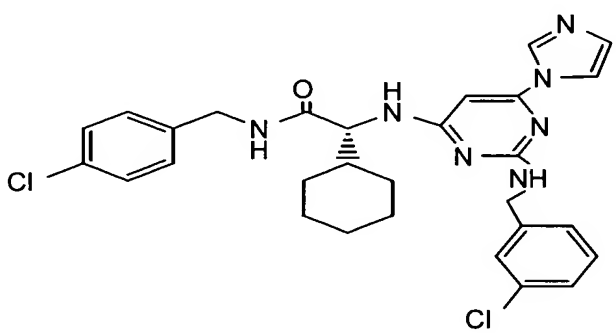
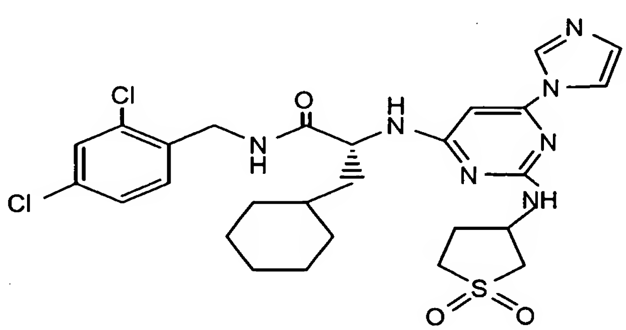
	696705
	525792
	848872
	081258

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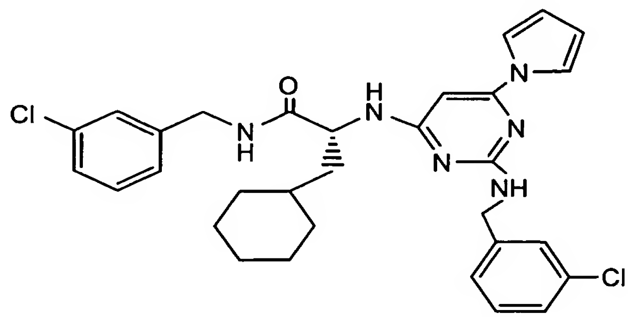
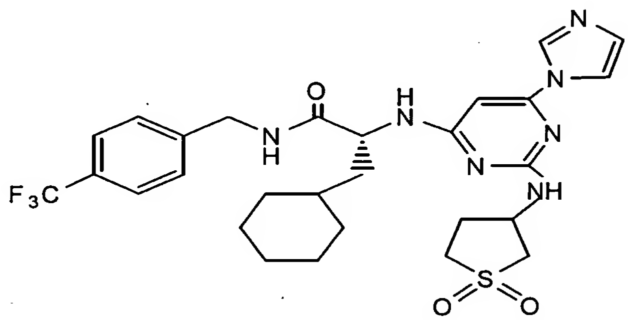
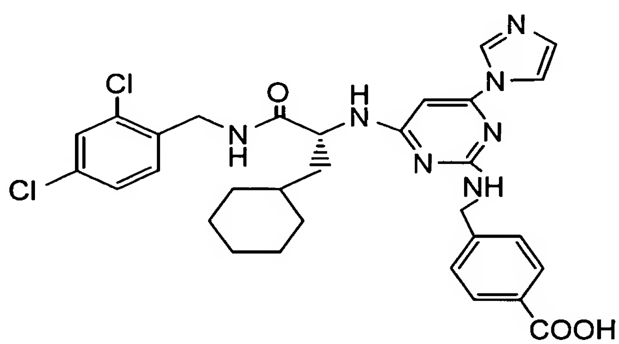
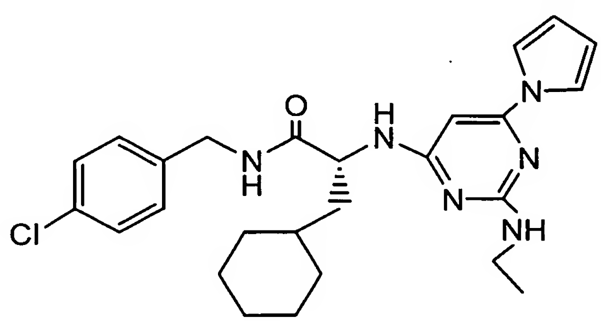
	599337
	579244
	271260 840374
	278223

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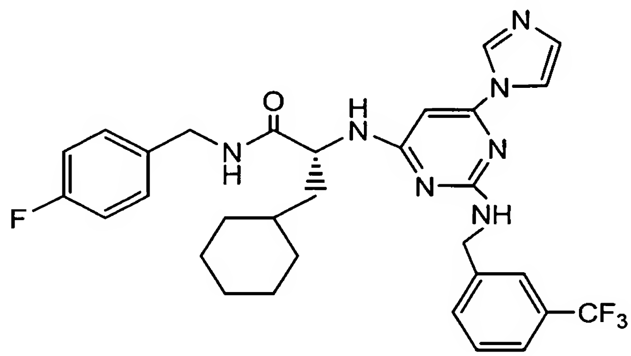
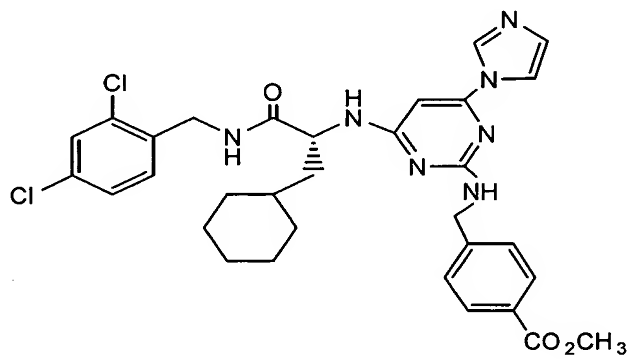
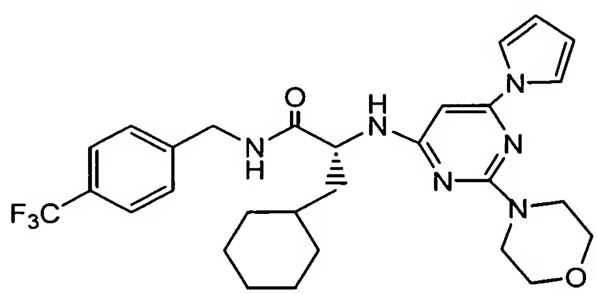
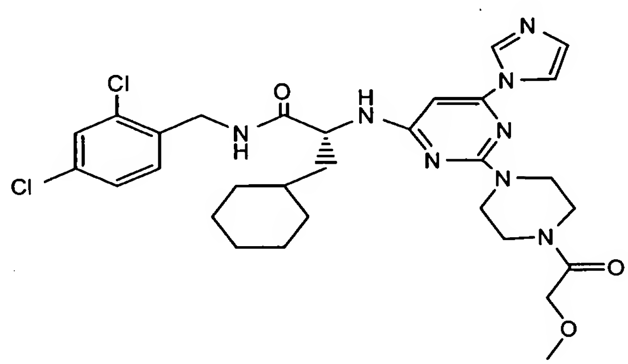
	020166
	683298
	595832
	306362

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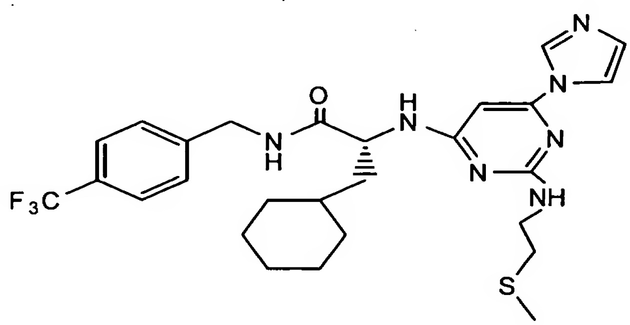
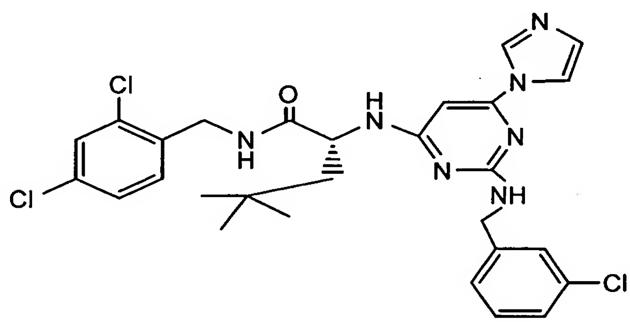
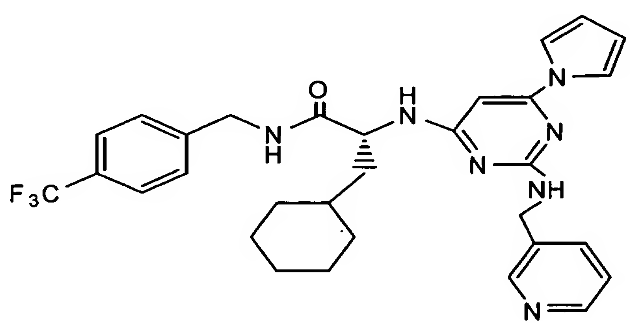
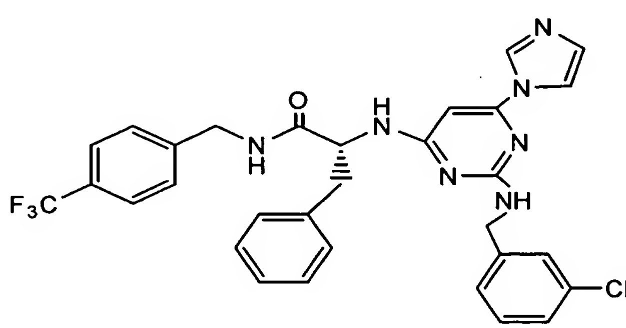
	464797
	391849
	056753
	778772

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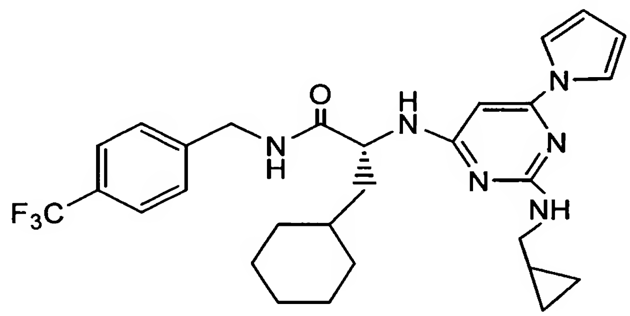
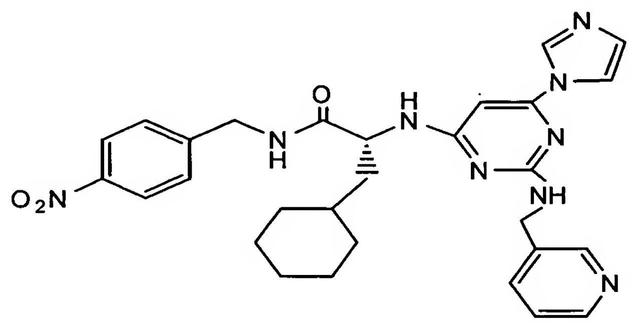
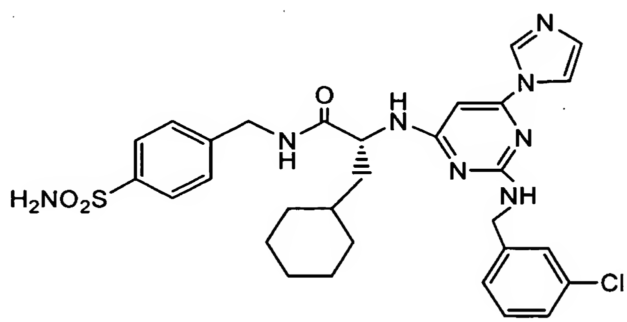
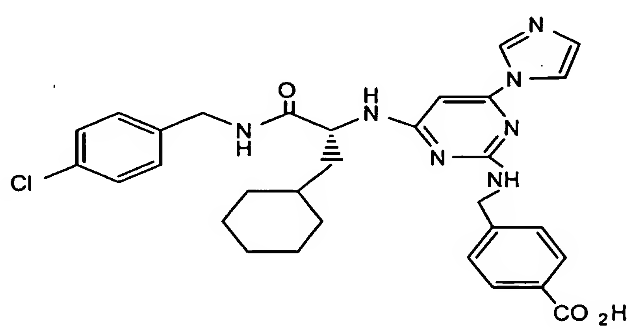
	190226
	481412
	862426
	417305

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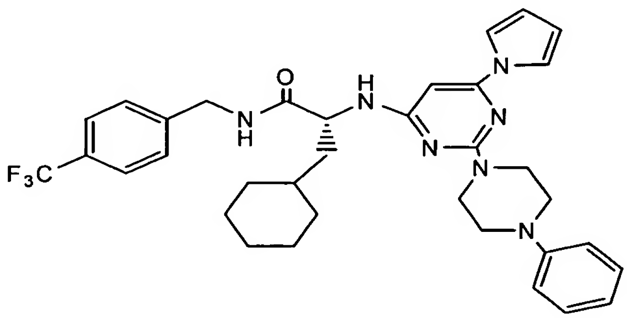
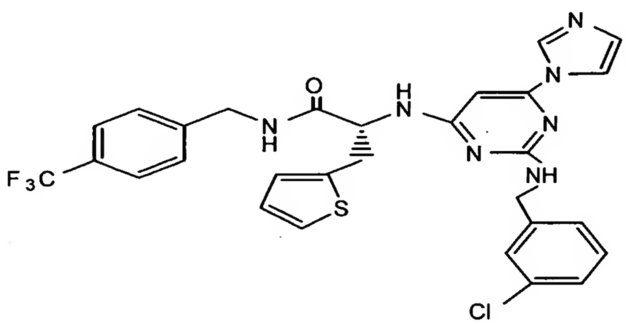
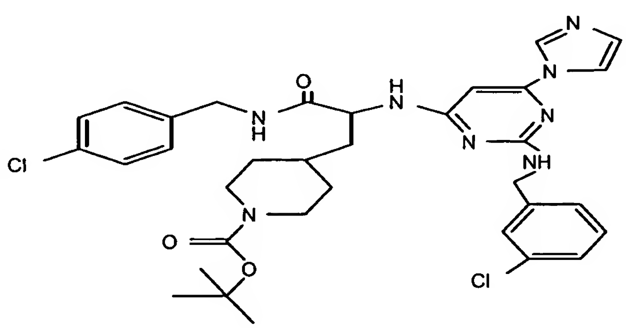
	311513
	678923
	333652

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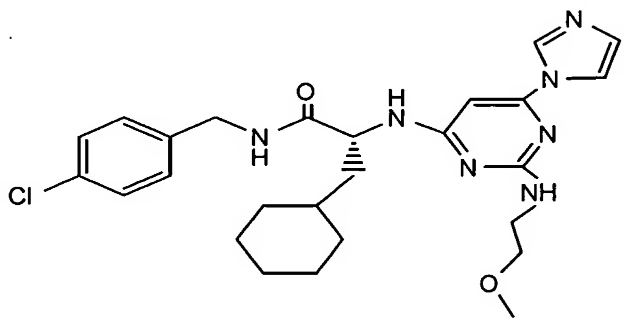
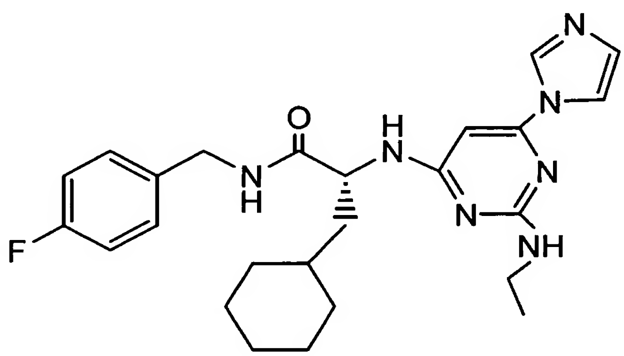
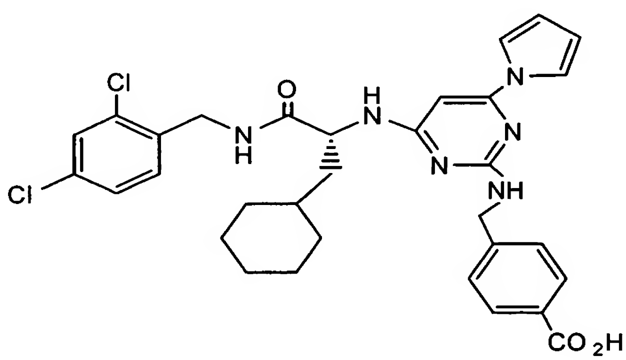
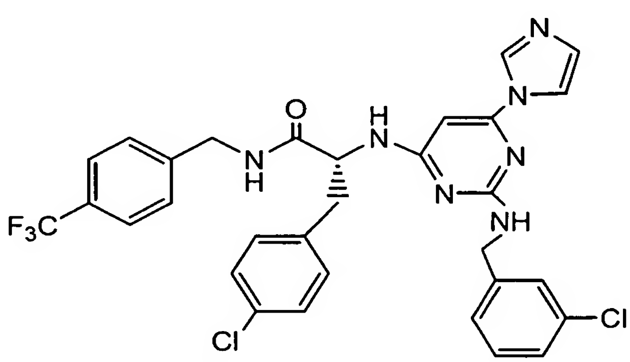
	614669
	700597
	533089
	912433

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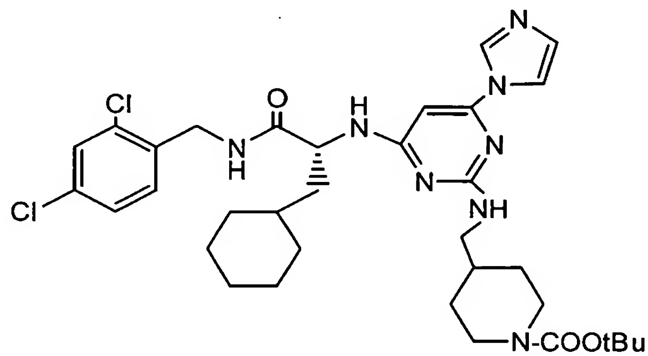
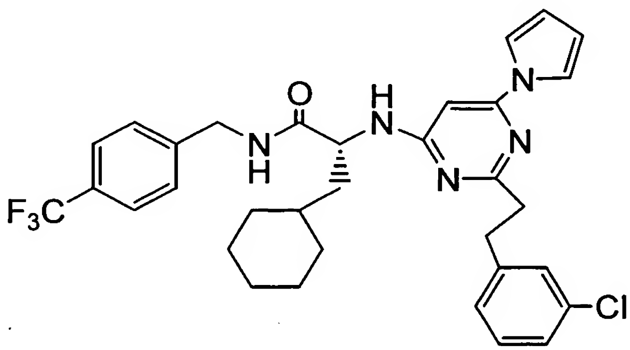
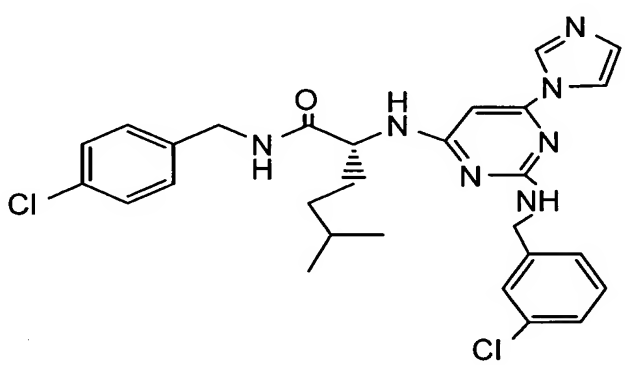
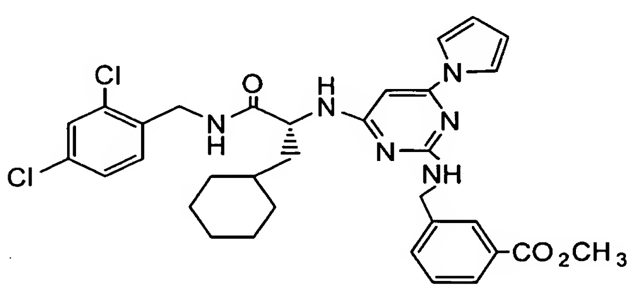
	292686
	082240
	296547
	917474

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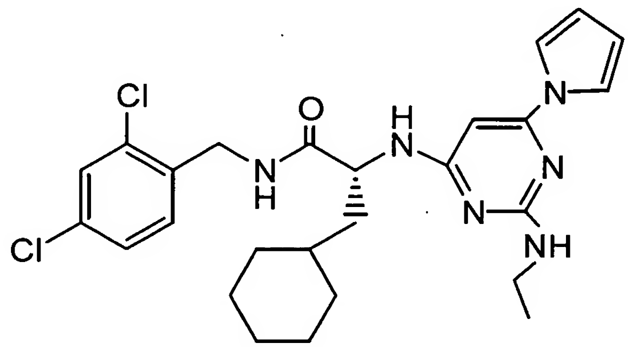
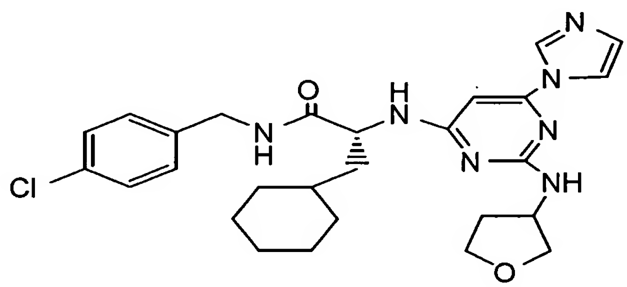
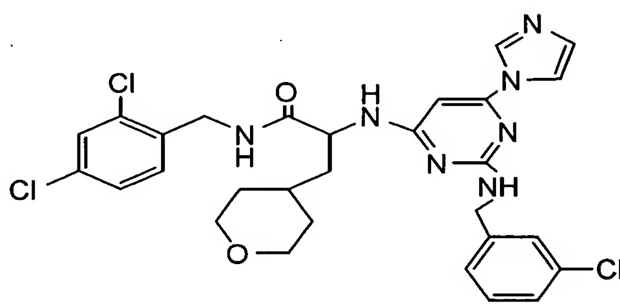
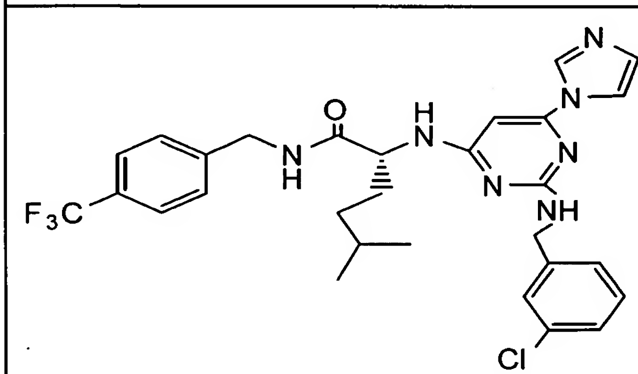
	923768
	482006
	040264
	917511

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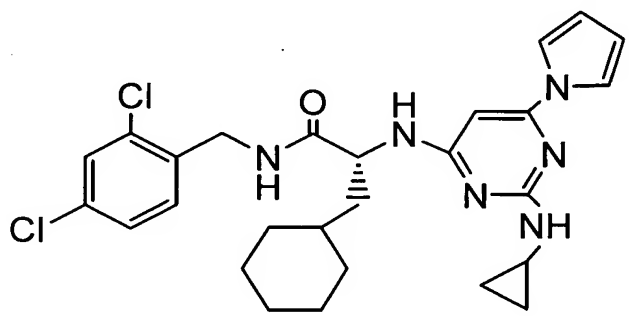
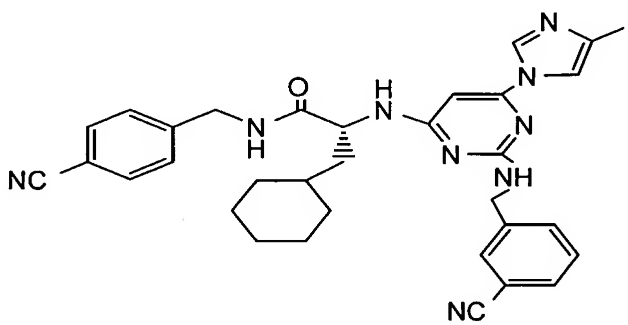
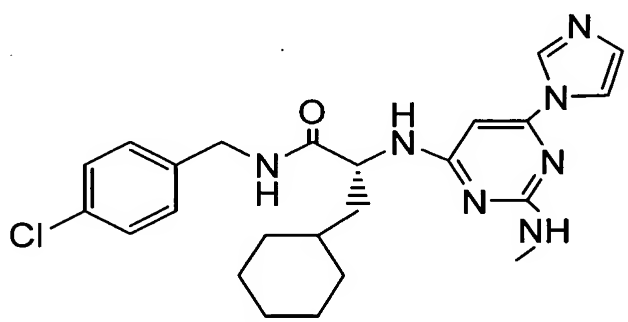
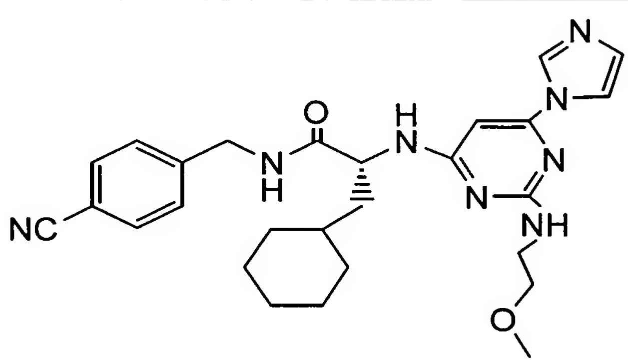
	559426
	552742
	489595
	045950

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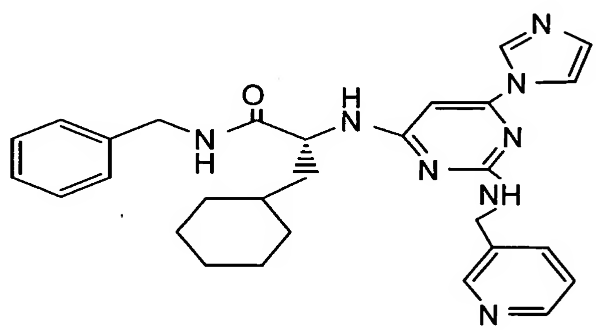
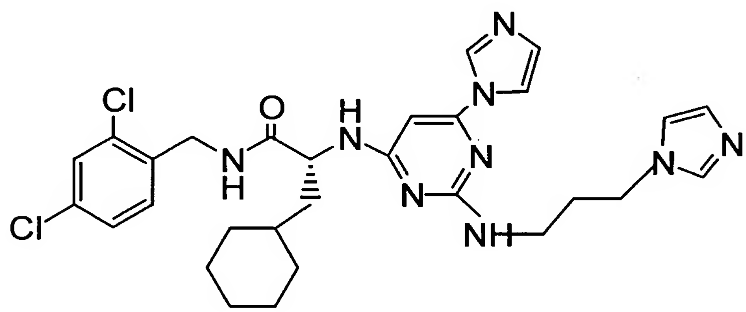
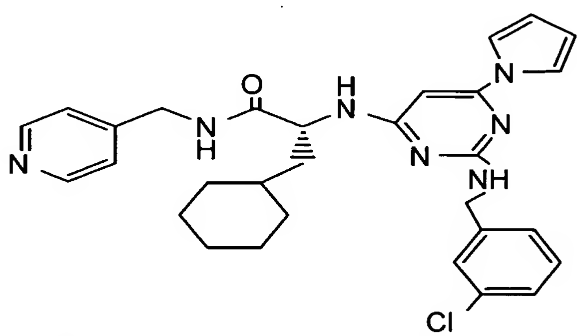
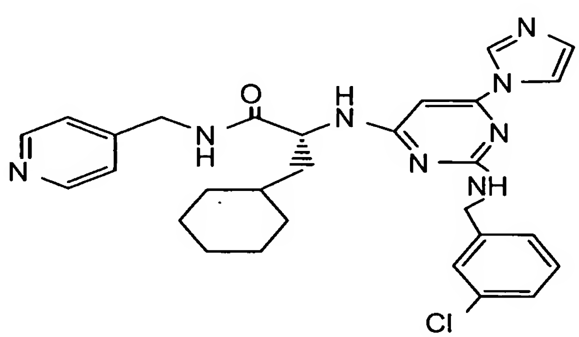
	070576
	251669
	167032
	190237

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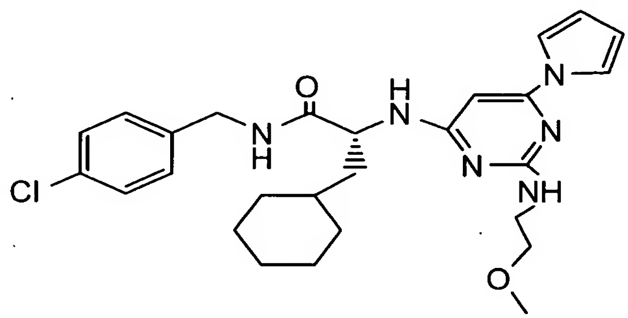
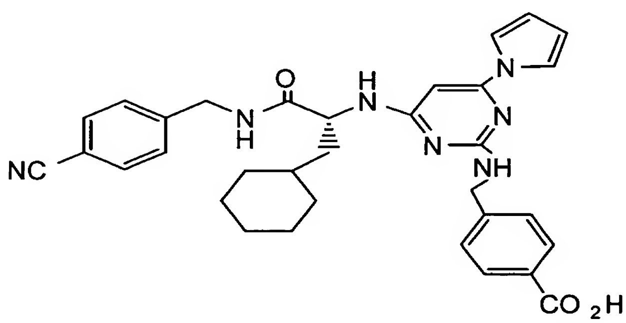
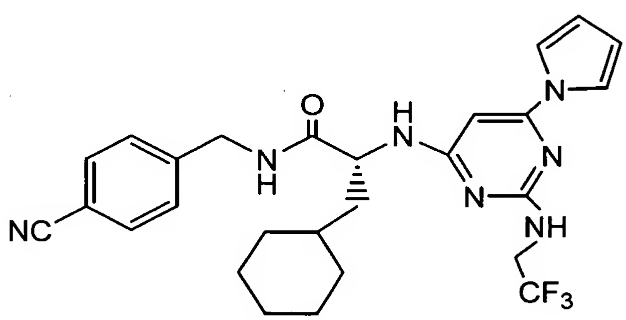
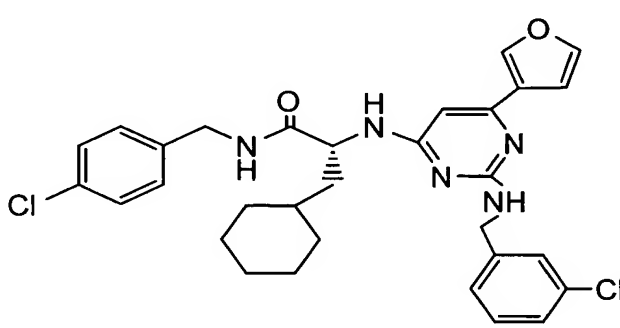
	307763
	832836
	310187
	369774

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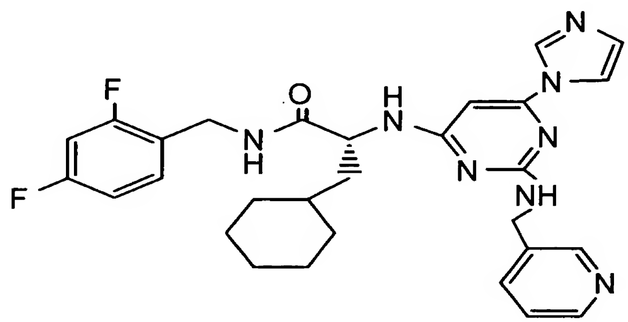
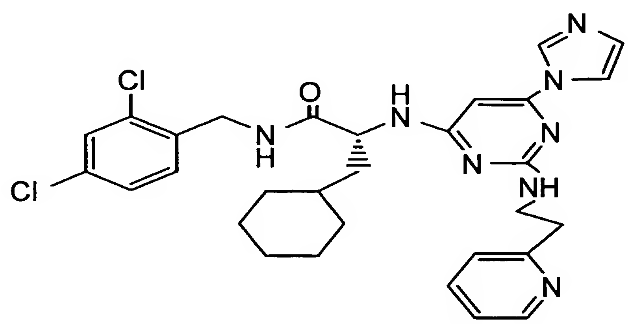
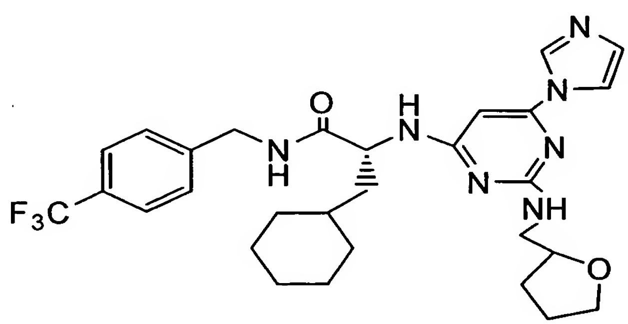
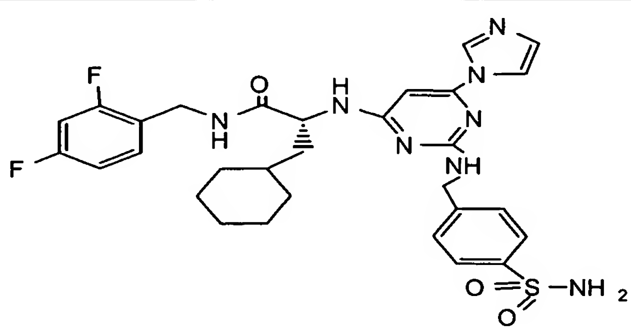
	833980
	191099
	087621
	288176

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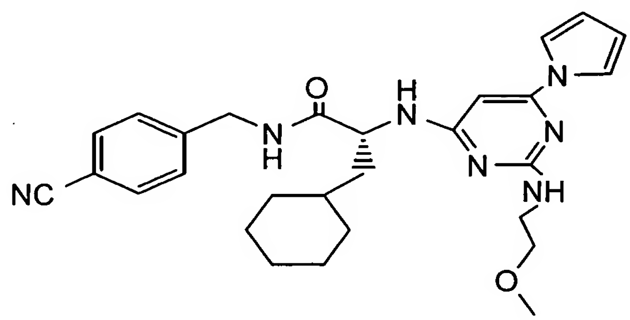
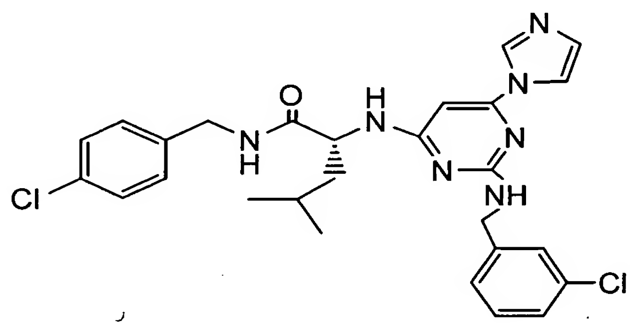
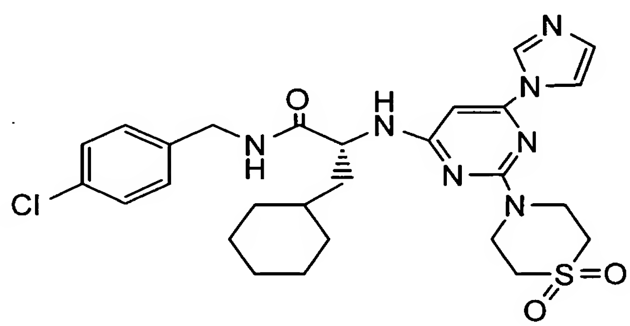
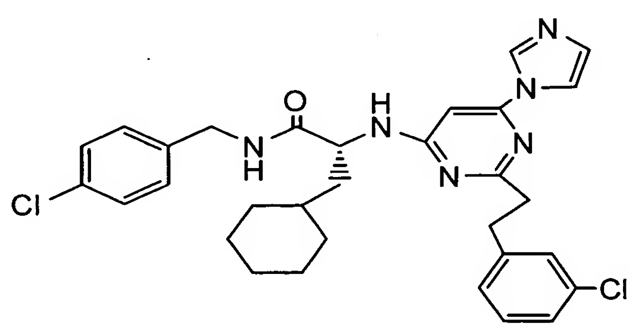
	630450
	714119
	124640
	506593

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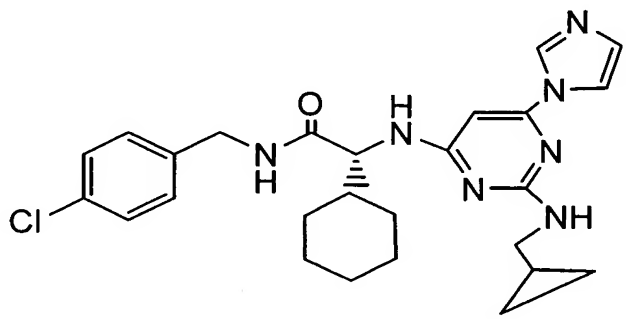
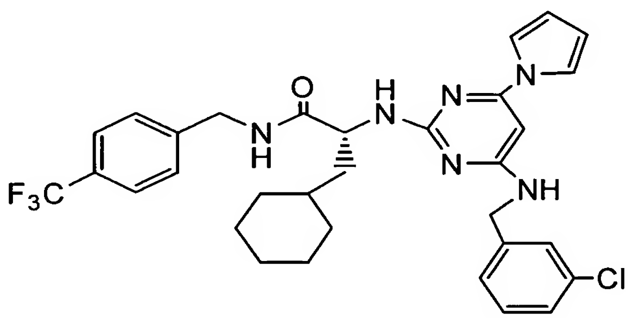
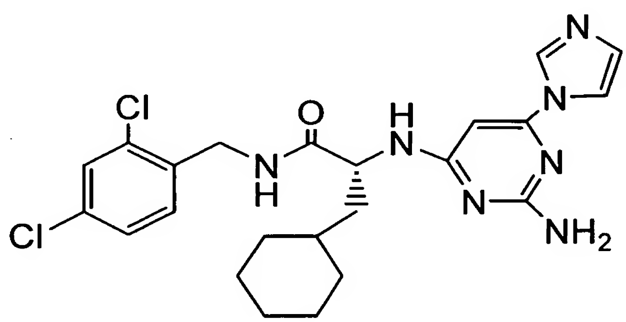
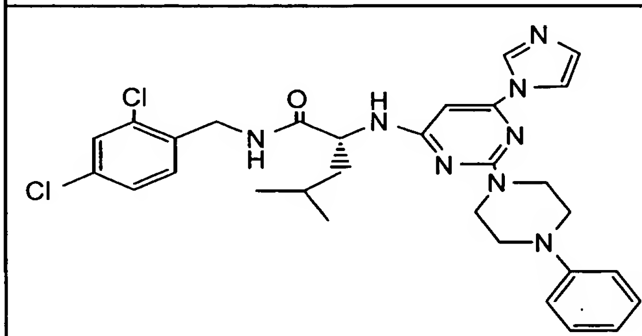
	340407
	036412
	884068
	768710

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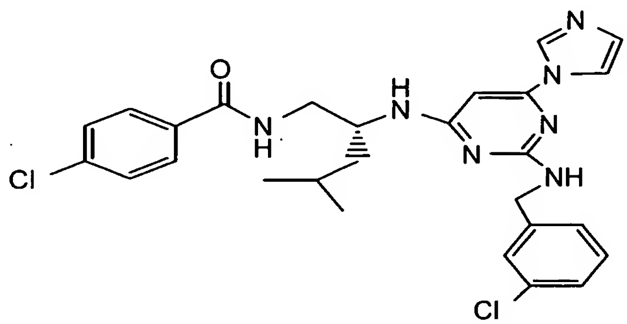
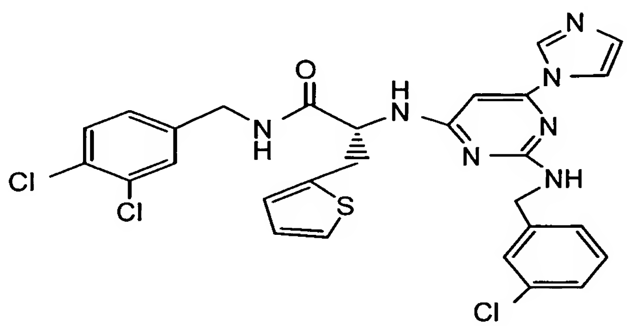
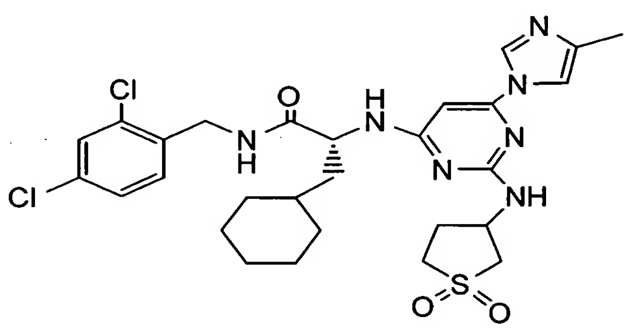
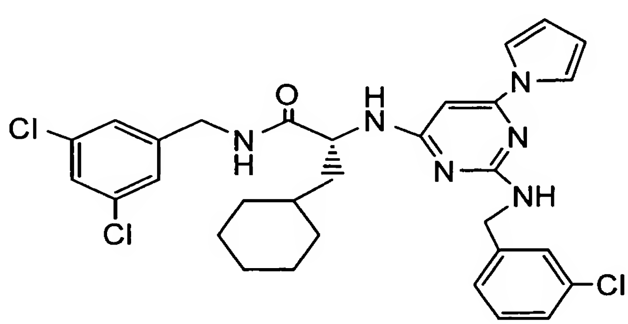
	207224
	221378
	183701
	389573

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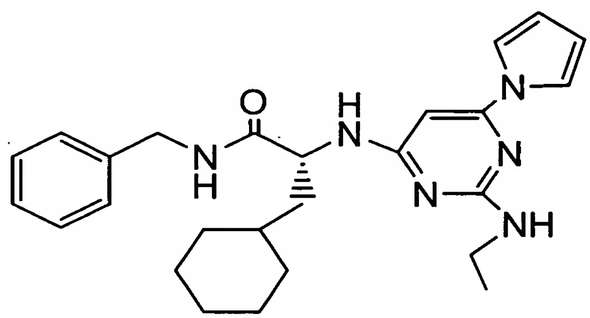
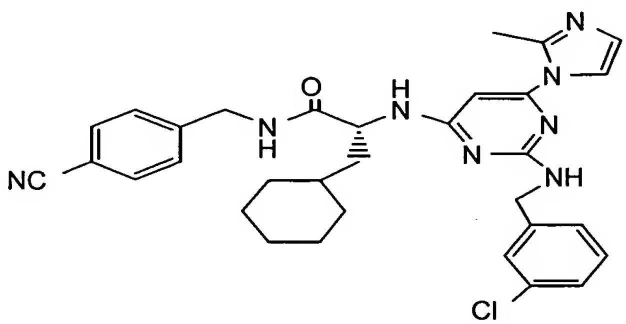
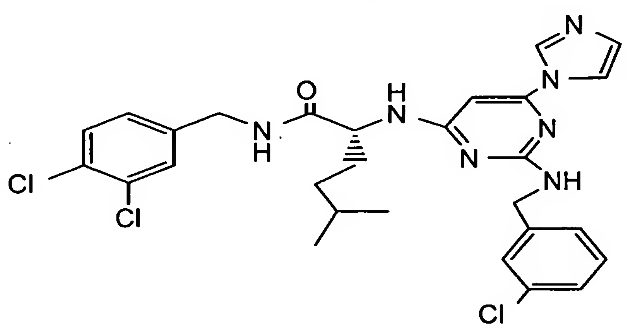
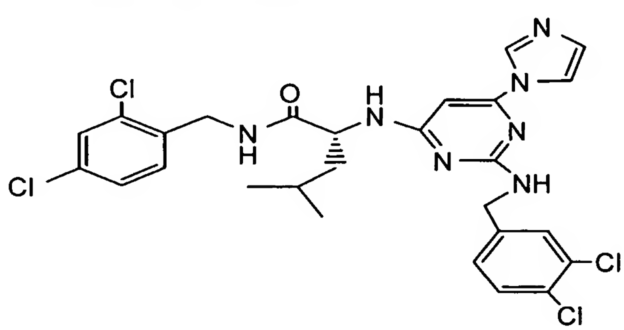
	936359
	019738
	736433
	604361

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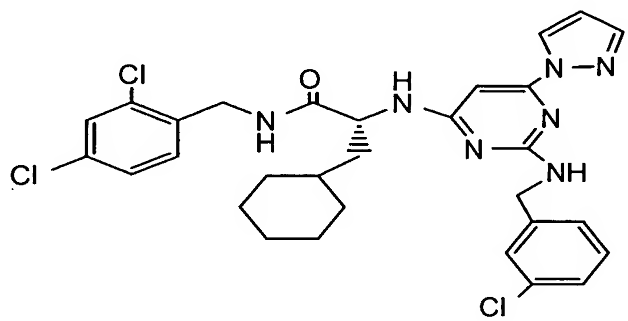
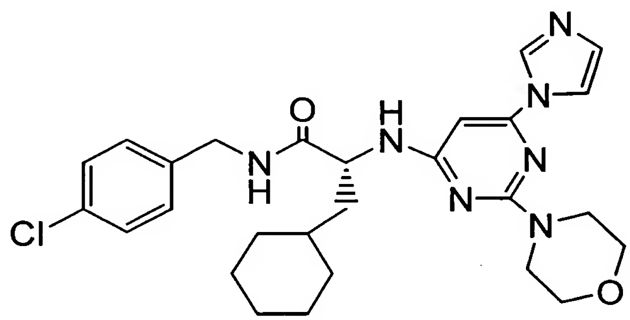
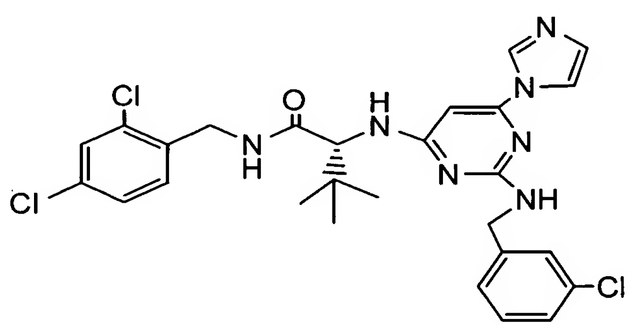
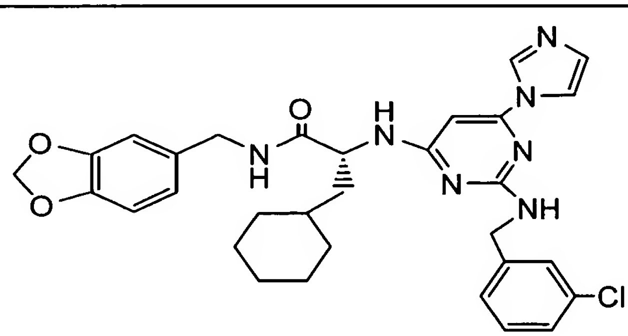
	125906
	638954
	186809
	614977

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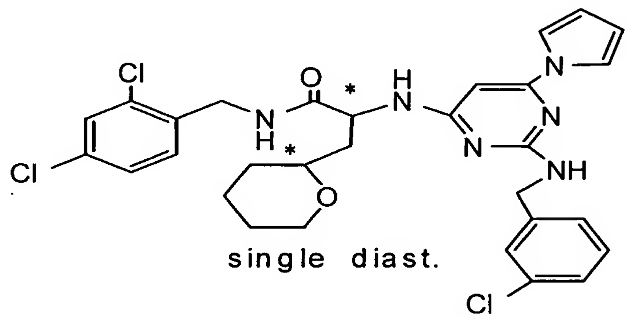
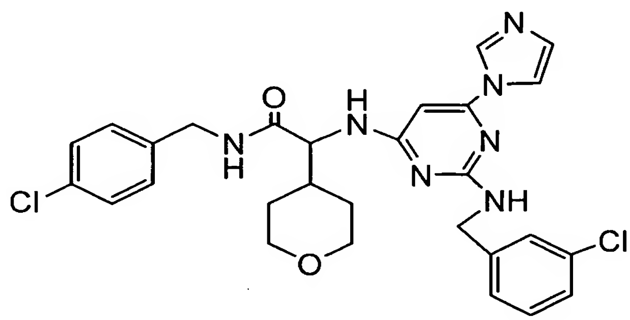
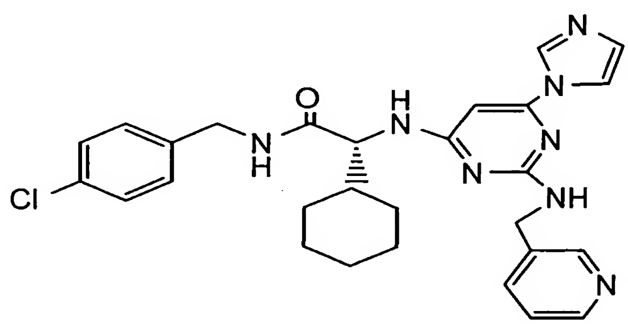
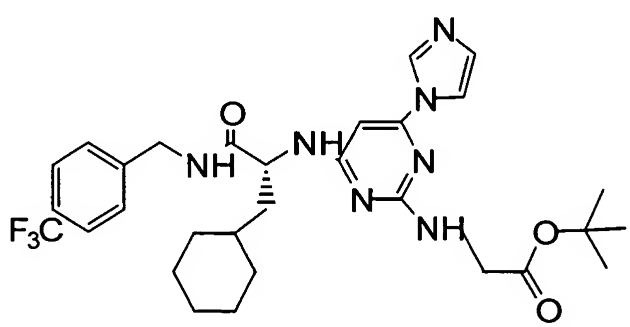
 single diast.	614250
	788826
	078208
	487103

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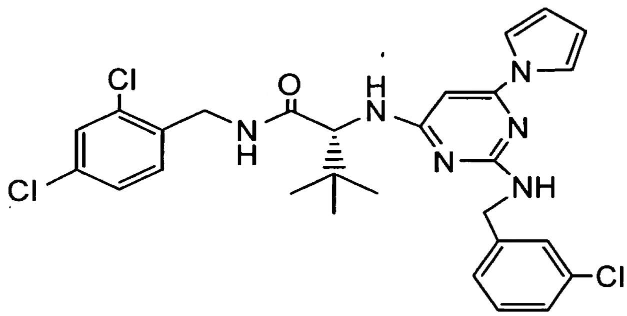
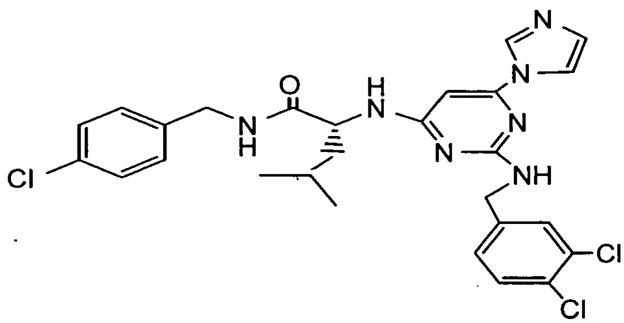
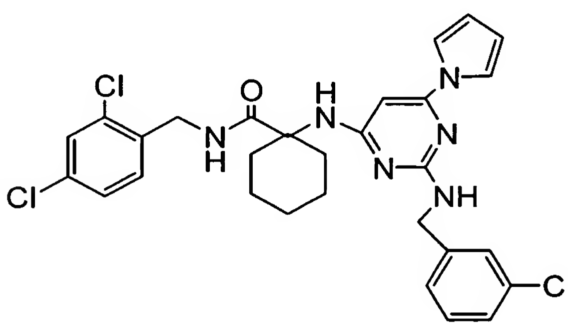
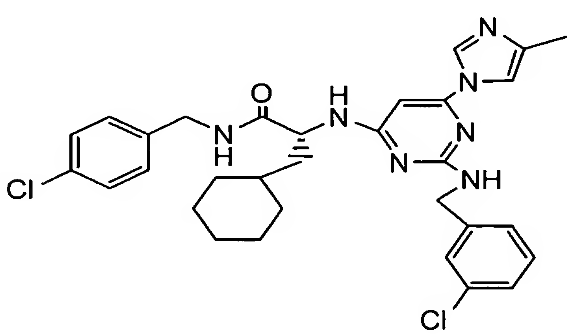
	542442
	634762
	191433
	319591

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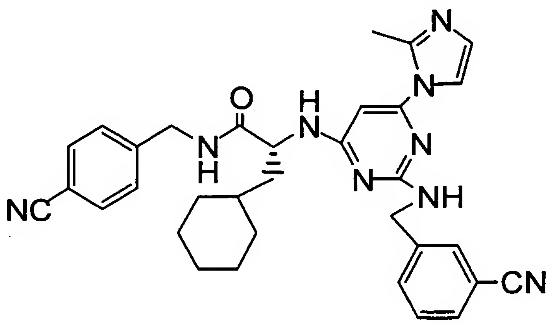
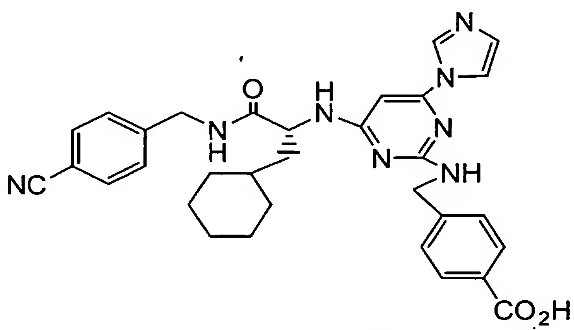
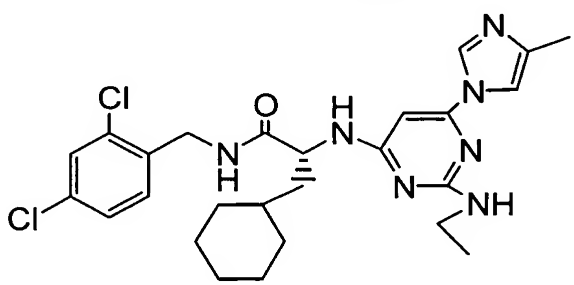
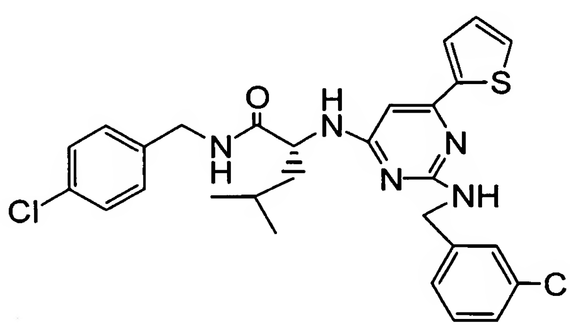
	841733
	814072
	235566
	959191

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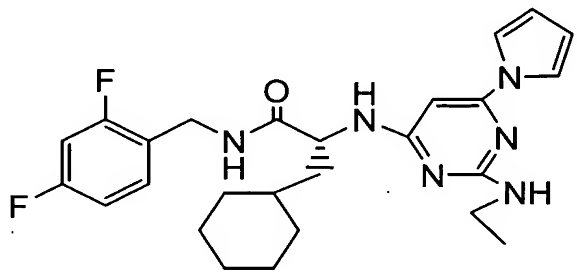
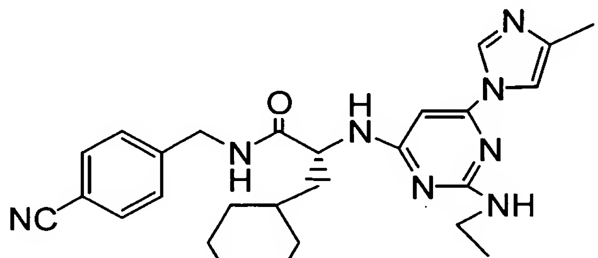
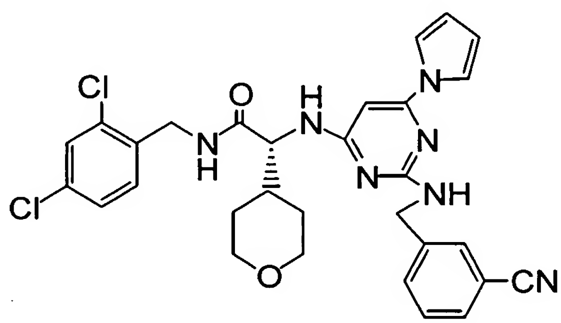
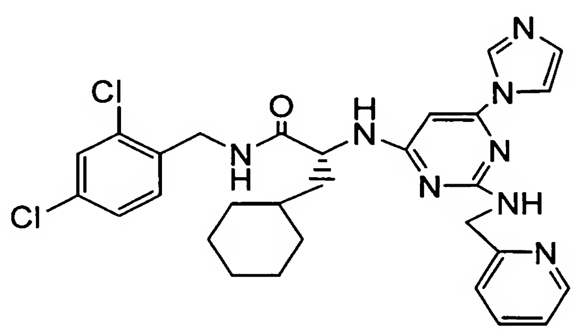
	812971
	037353
	105995
	629668

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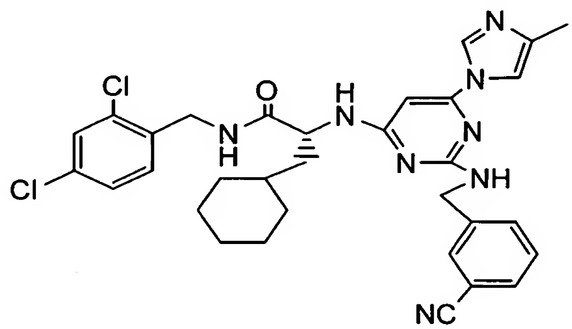
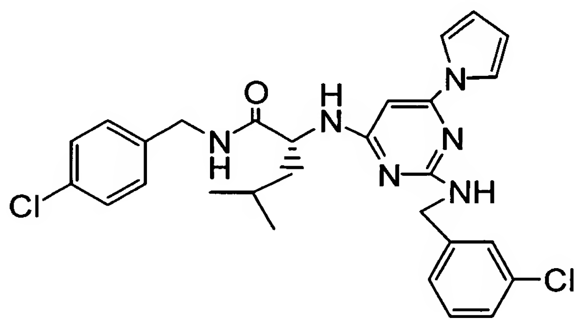
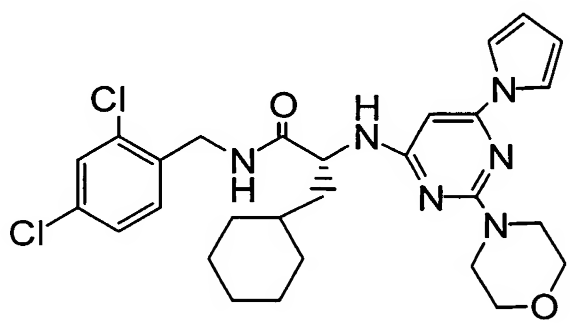
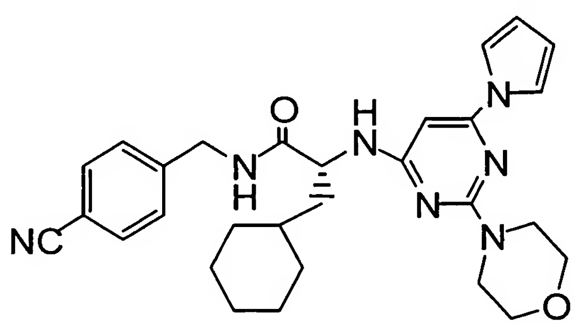
	159661
	081752
	696652
	312958

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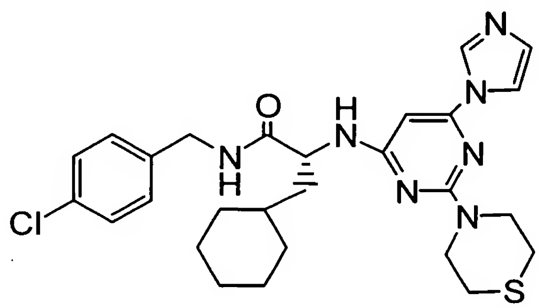
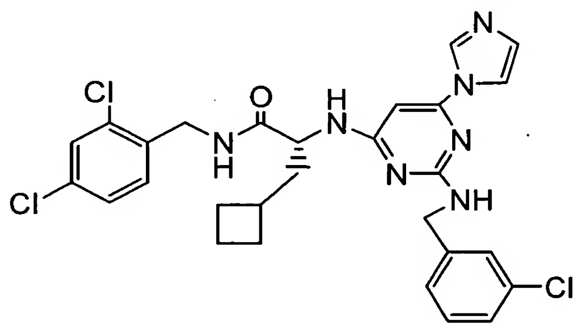
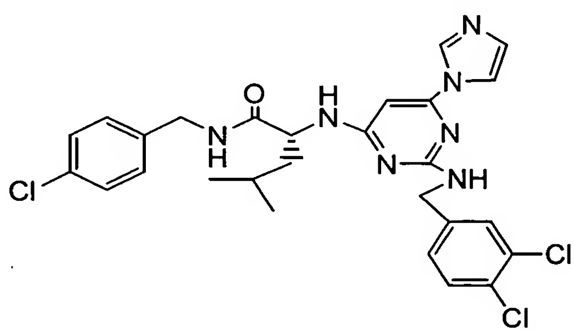
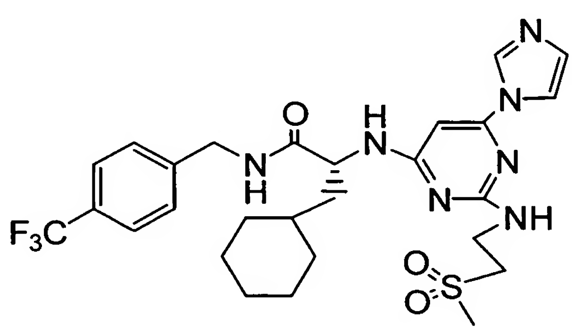
	757098
	223929
	930464
	391100

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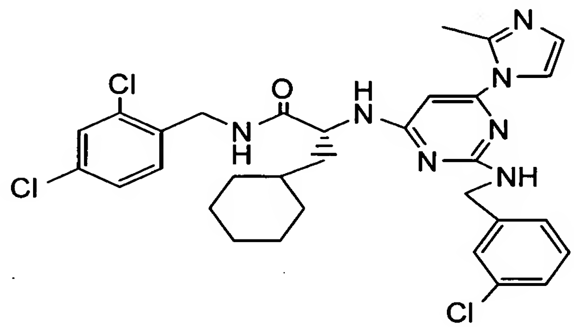
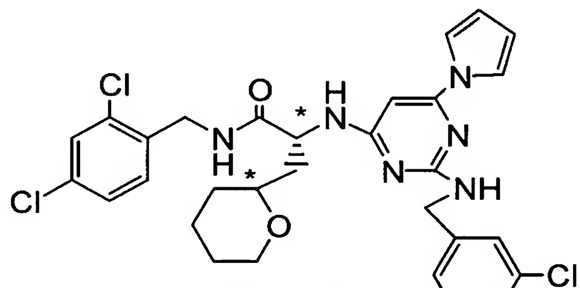
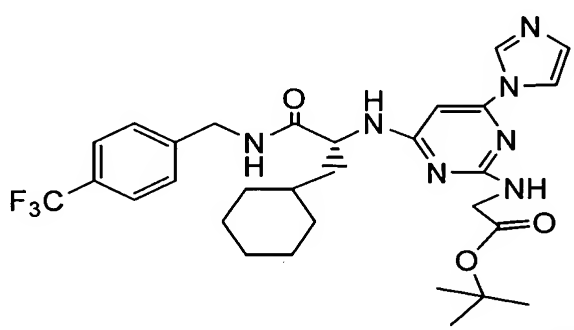
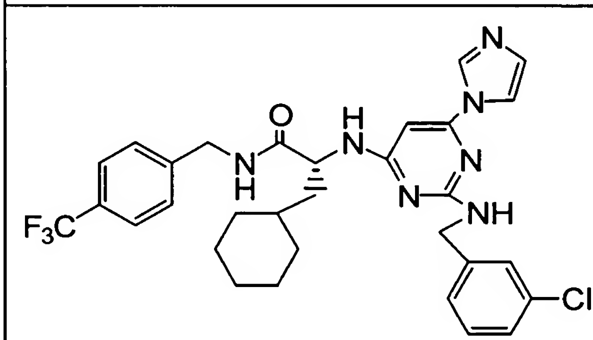
	337128
 single diast.	185383
	769887
	532528

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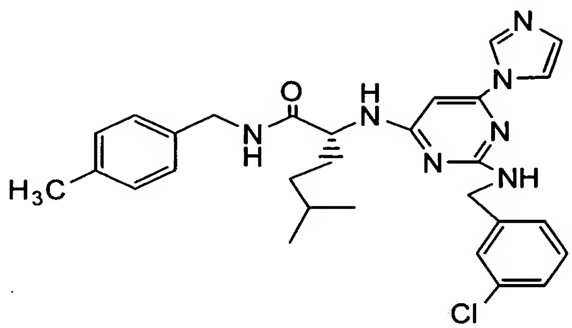
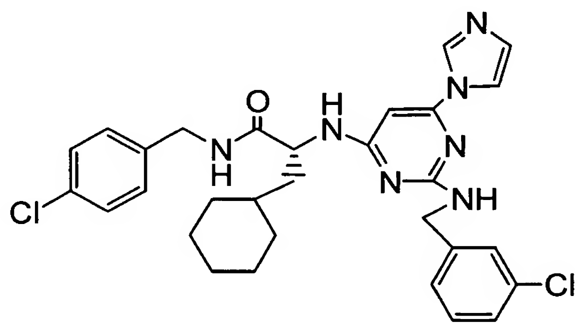
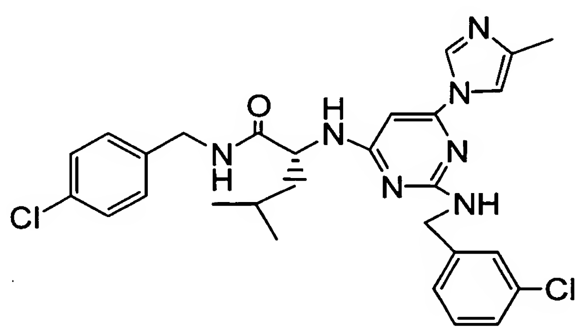
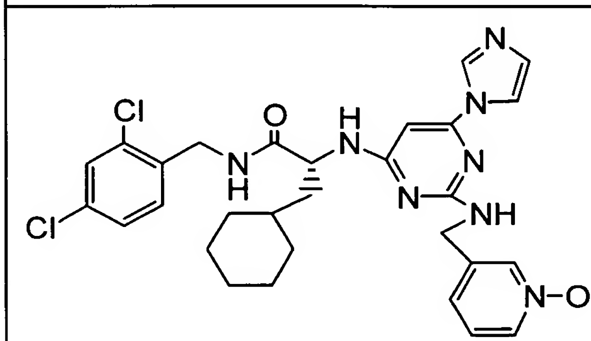
	817699
	702309
	888316
	578730

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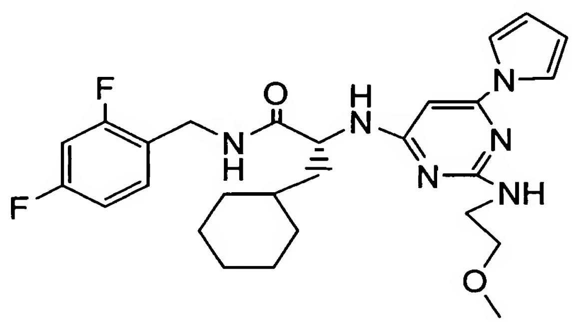
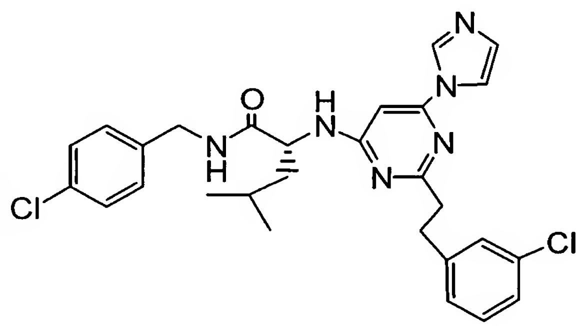
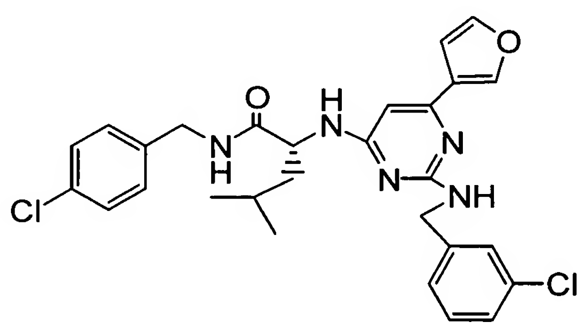
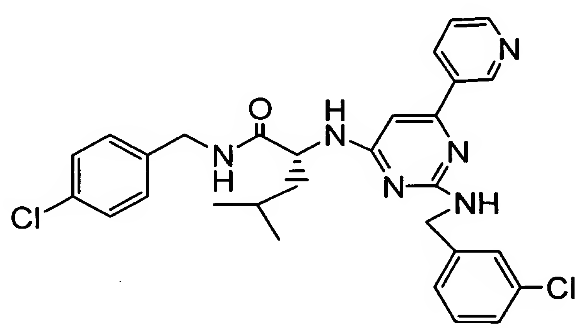
	917717
	326011
	794377
	905178

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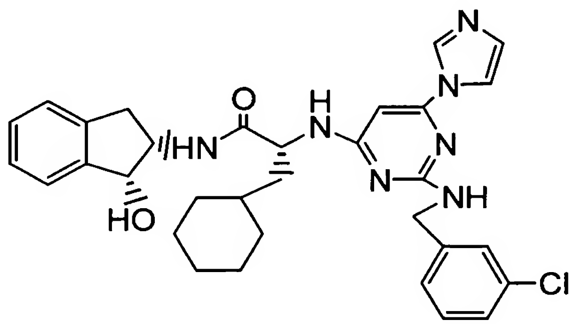
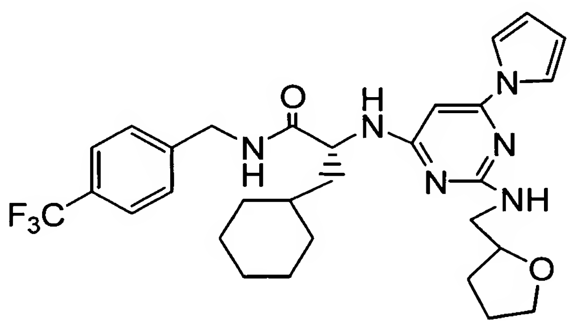
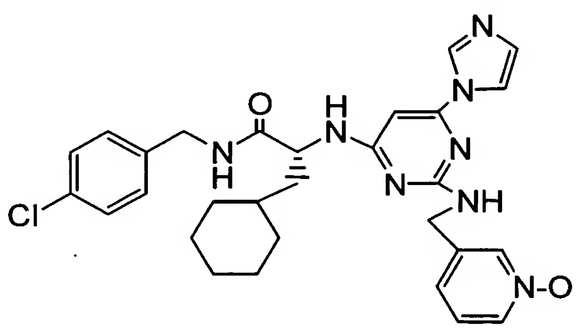
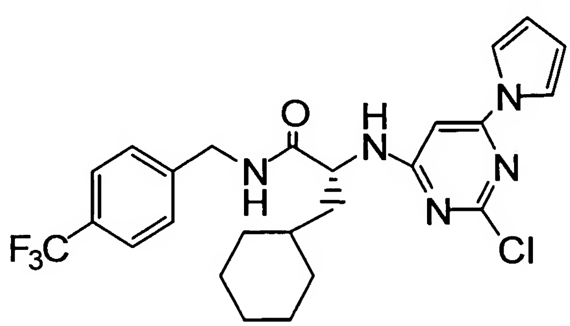
	573817
	598738
	857482
	663495

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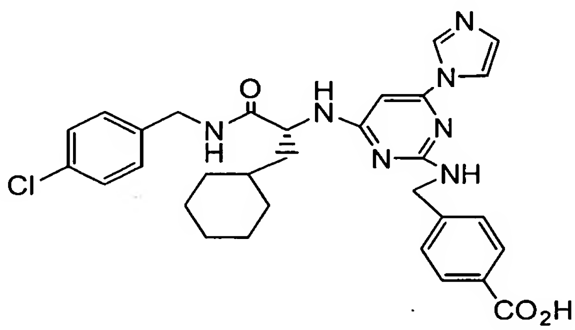
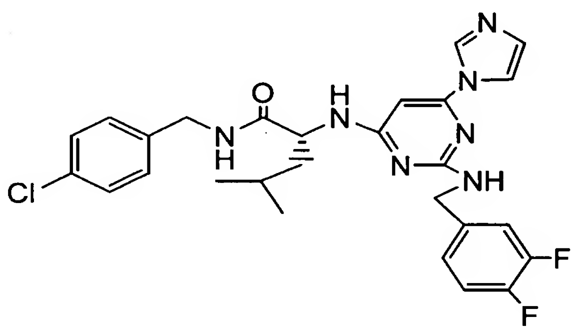
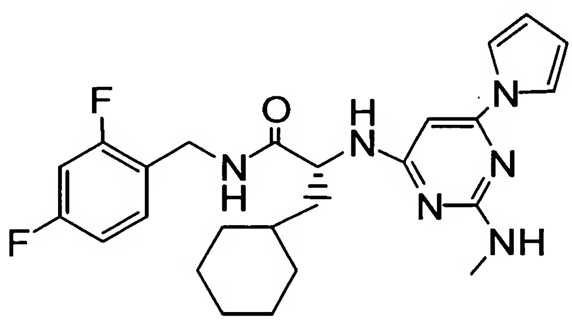
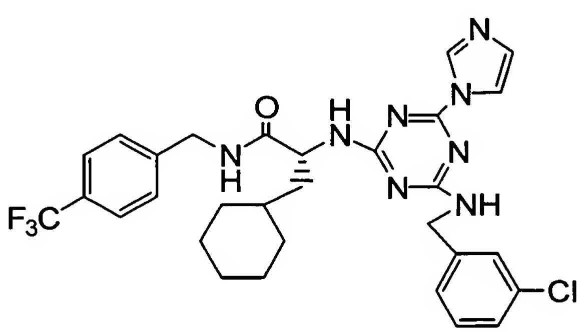
	991312
	225992
	926424
	339394

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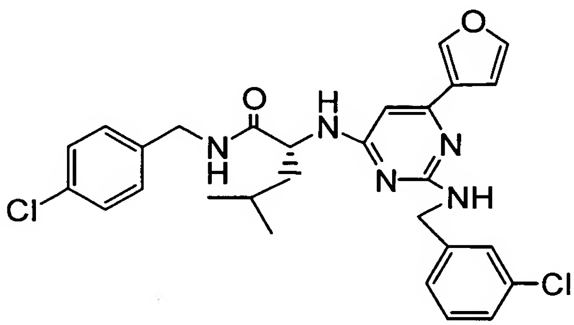
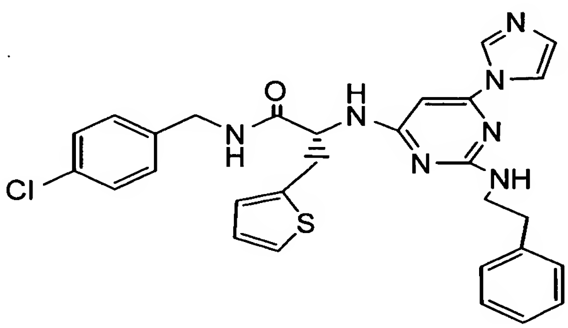
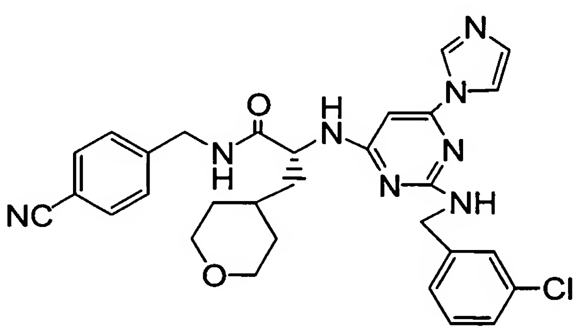
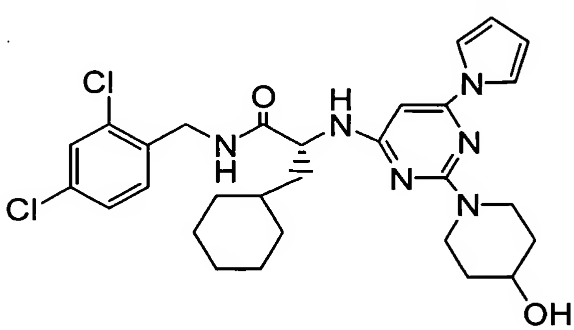
	781549
	566540
	584062
	615004

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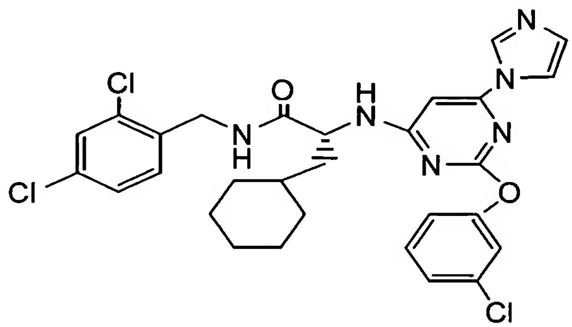
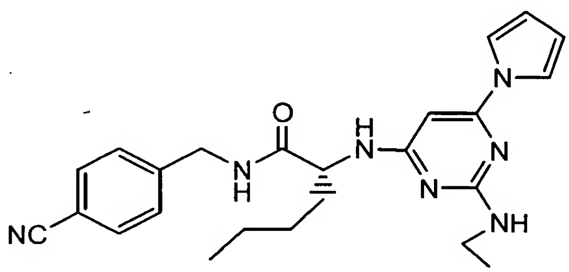
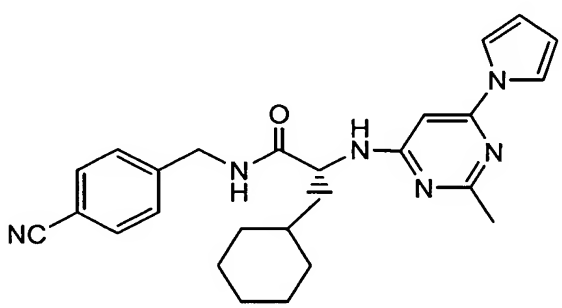
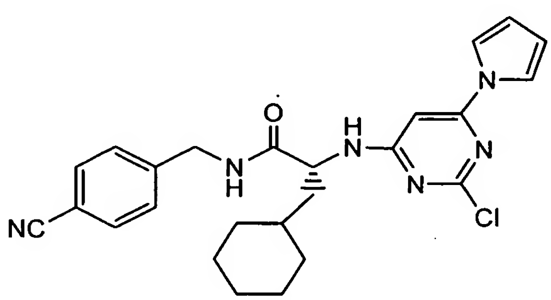
	098519
	815097
	360639
	828037

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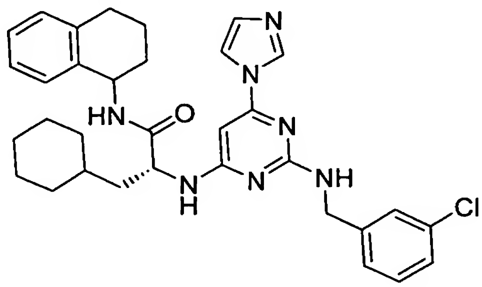
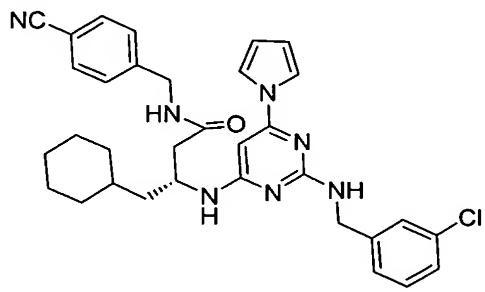
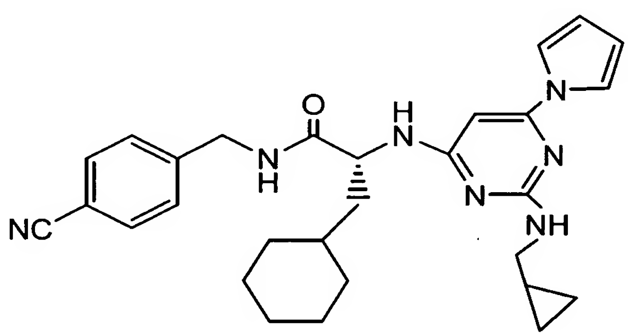
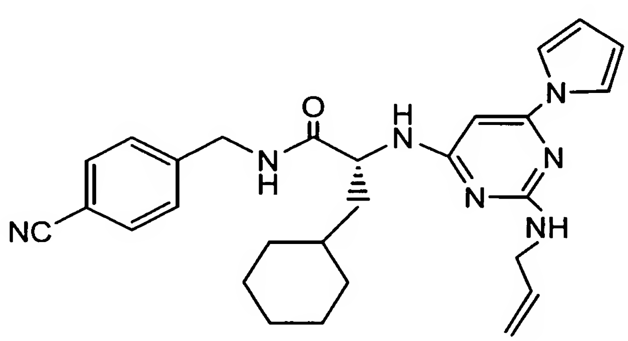
	972282
	080030
	811358
	097881

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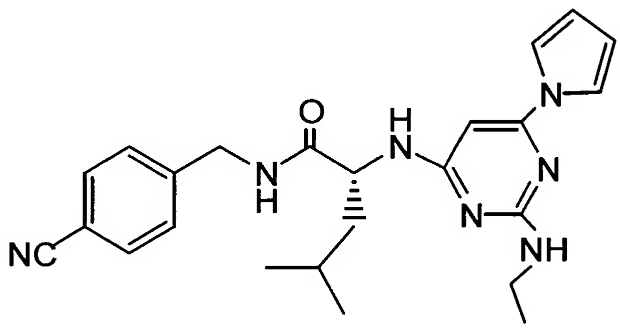
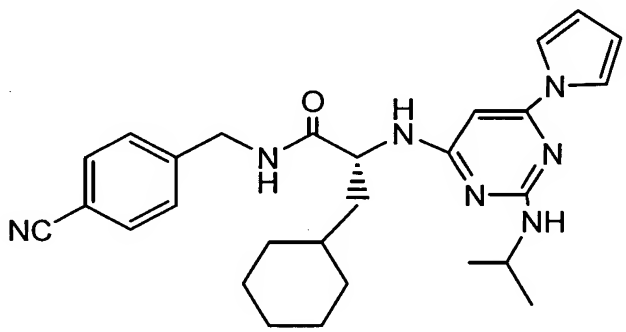
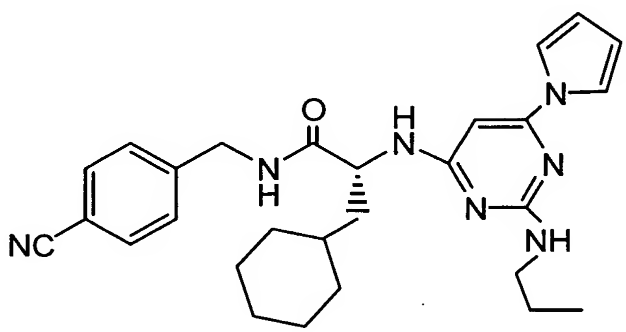
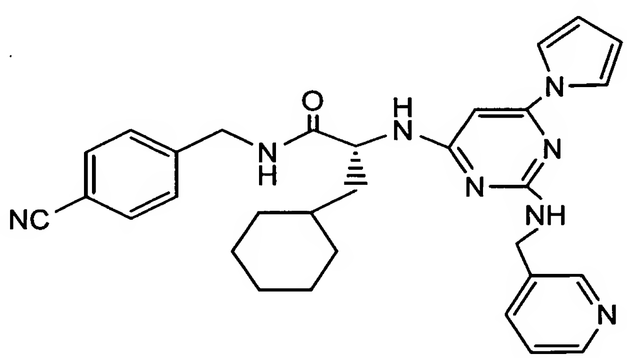
	270821
	655480
	713653
	091950

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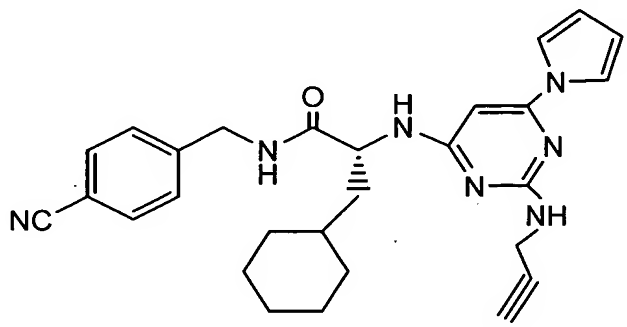
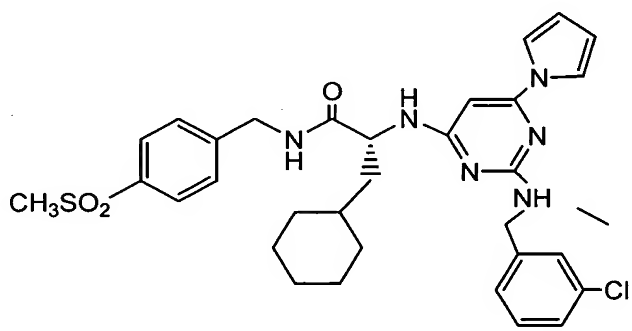
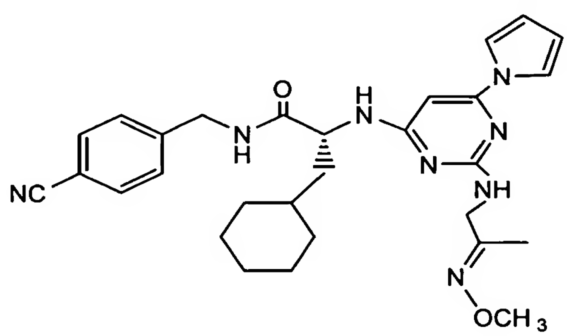
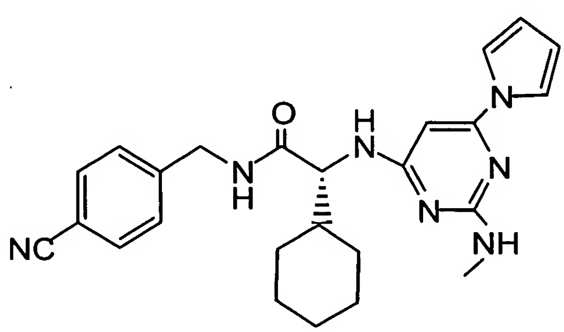
	014922
	556200
	936852
	167307

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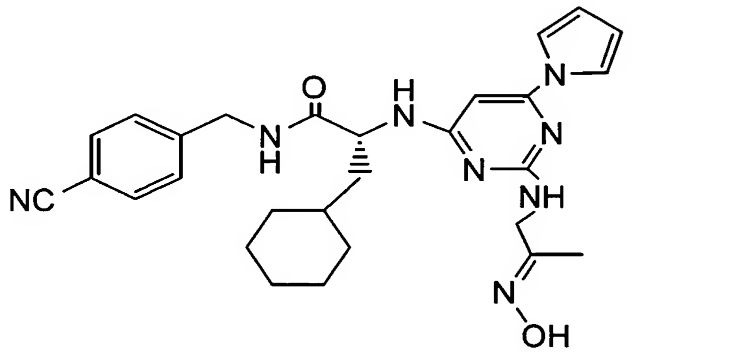
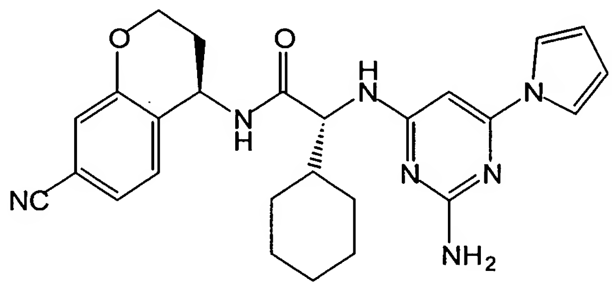
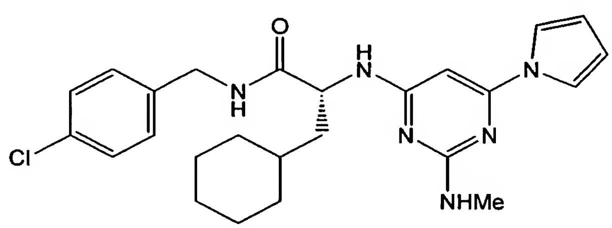
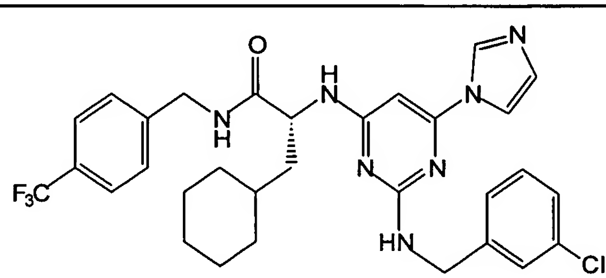
	218245
	424569
	307763
	532528

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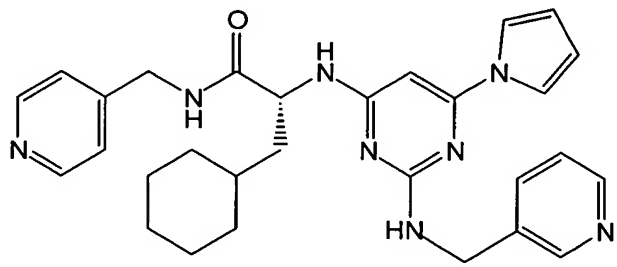
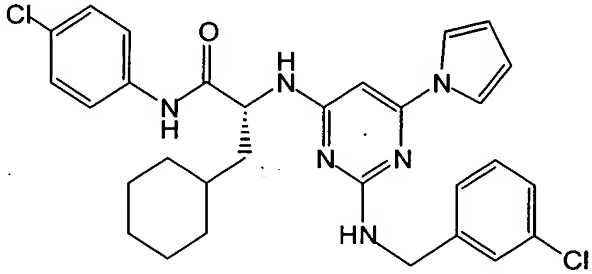
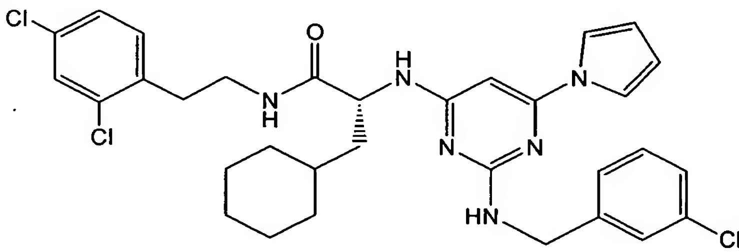
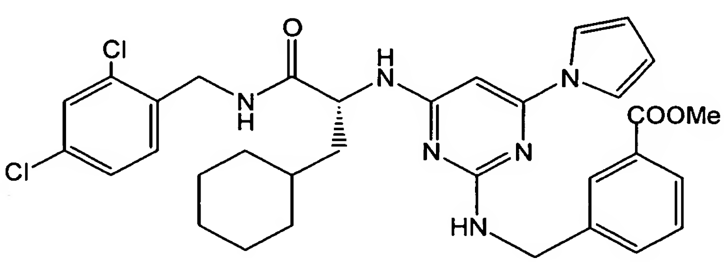
	997039
	599337
	389573
	919044

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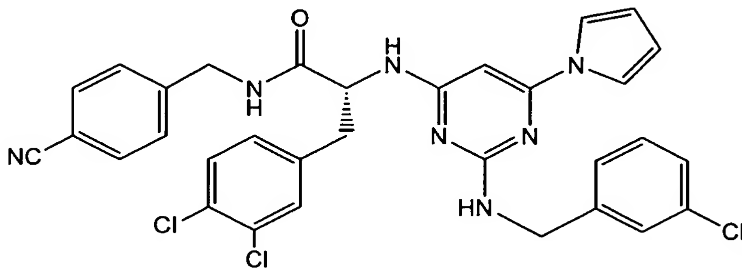
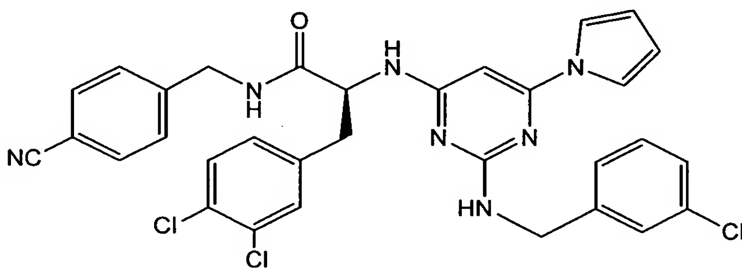
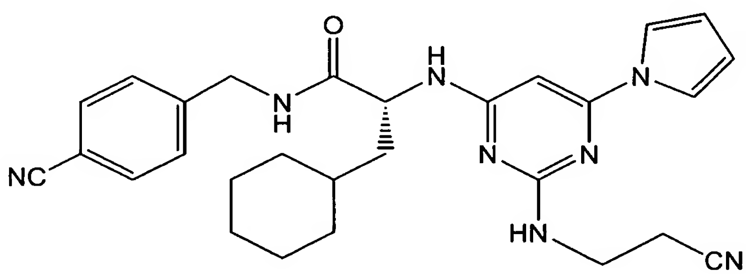
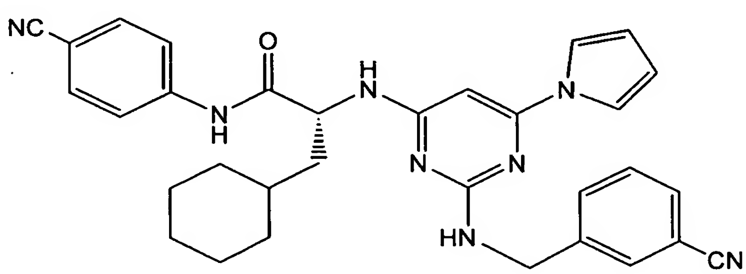
	091217
	813326
	592843
	053116

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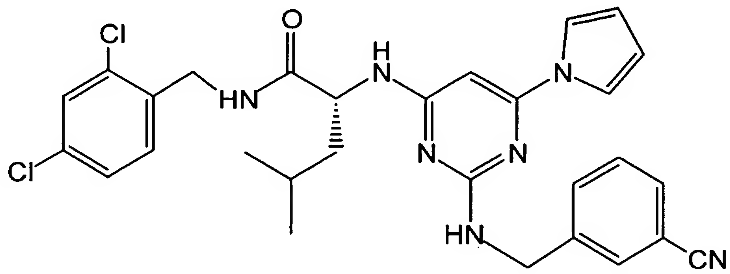
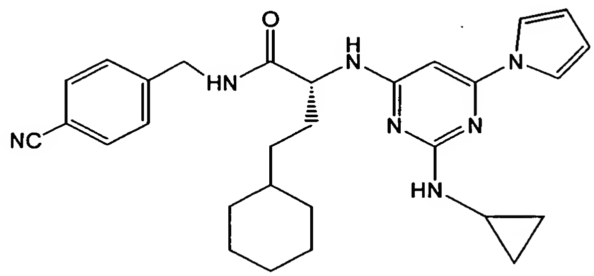
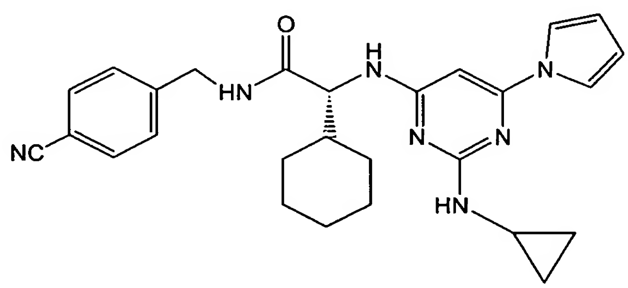
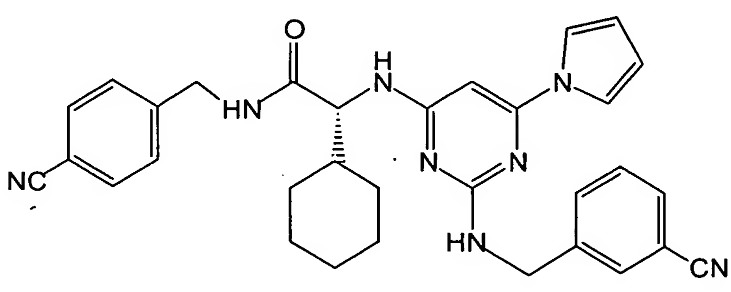
	416383
	762112
	788965
 956568	

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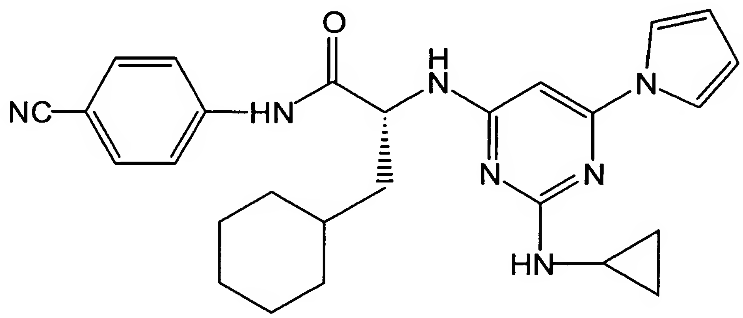
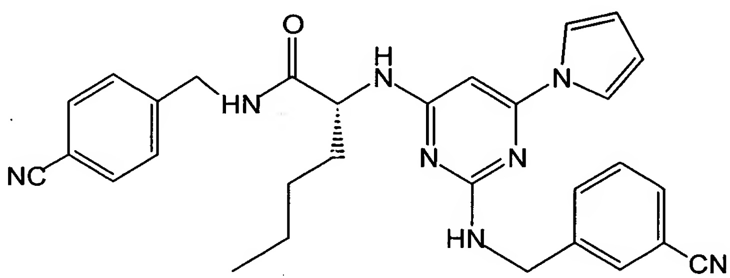
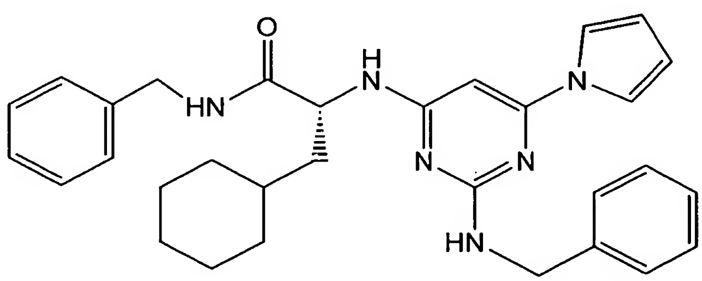
	592995
	642706
	916924

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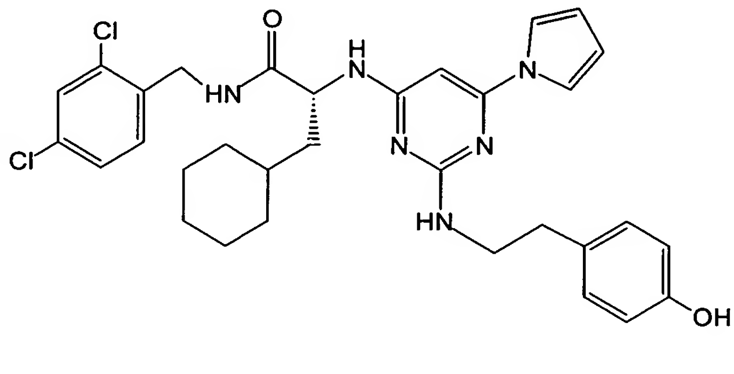
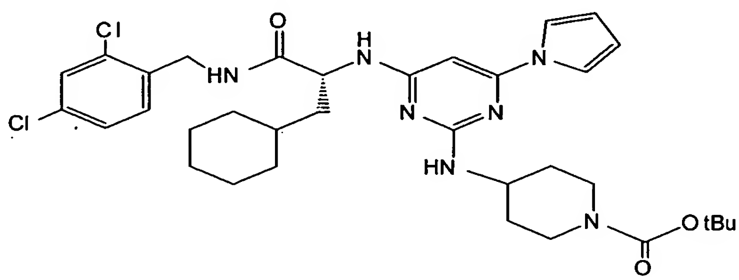
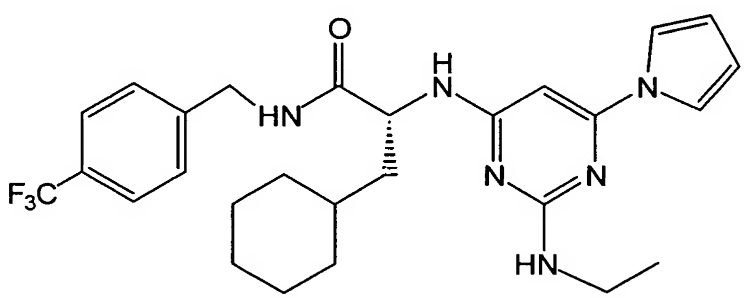
	406896
	463621
	103379

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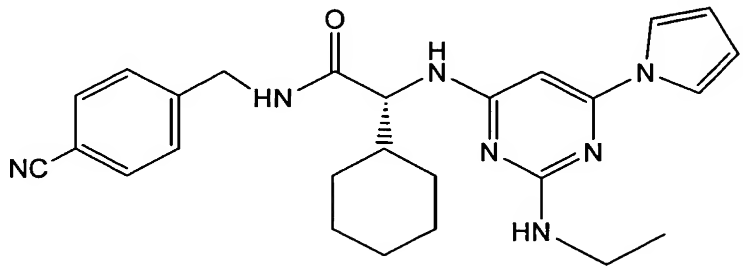
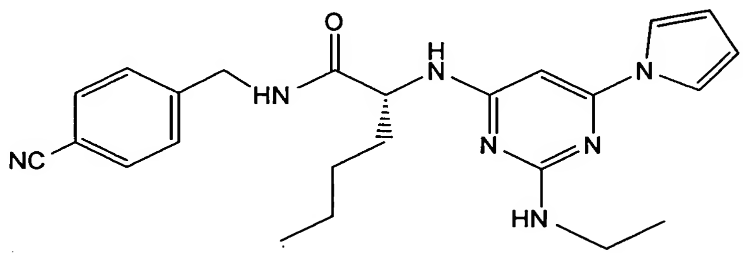
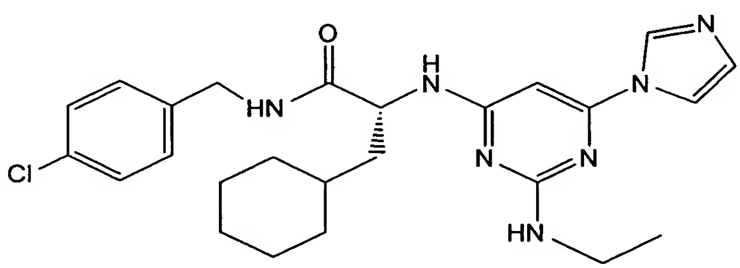
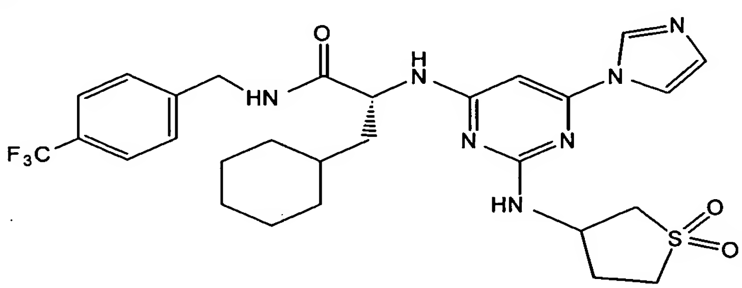
	073408
	815097
	115870
	579244

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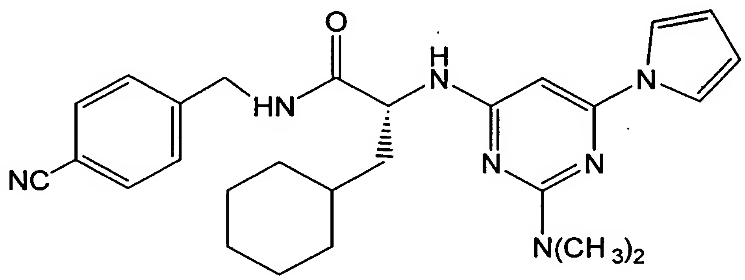
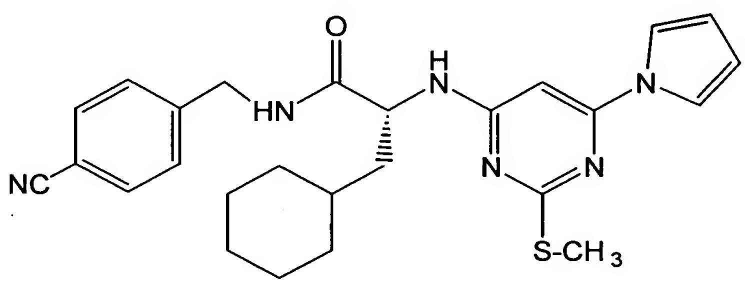
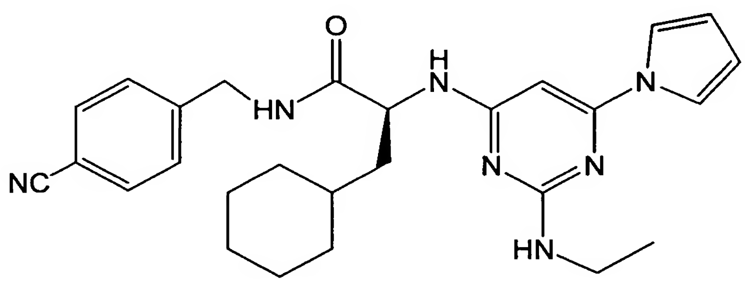
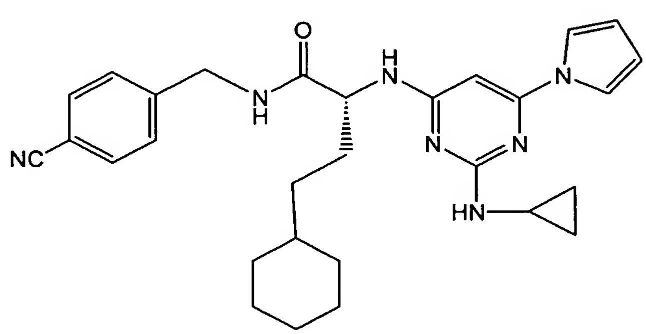
	551184
	194859
	934834
	762112

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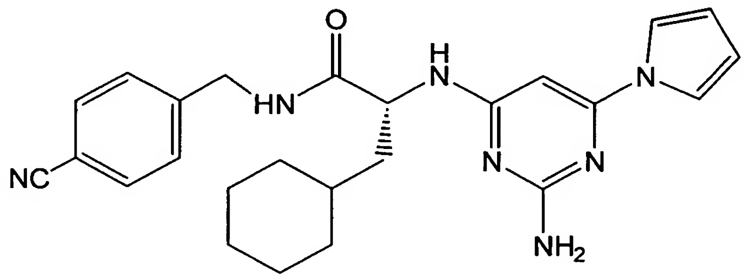
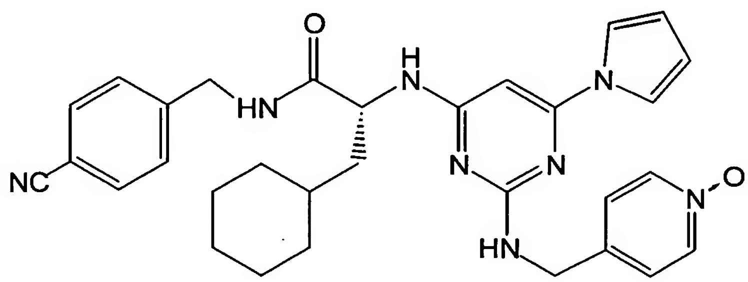
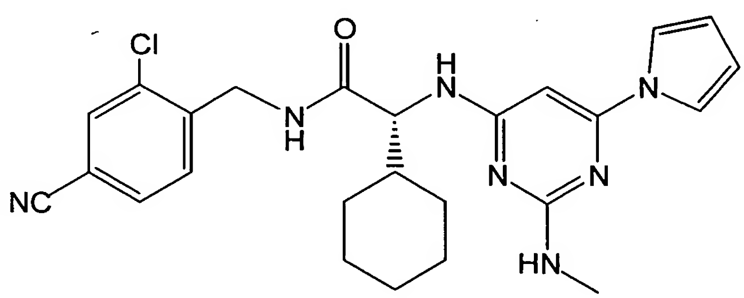
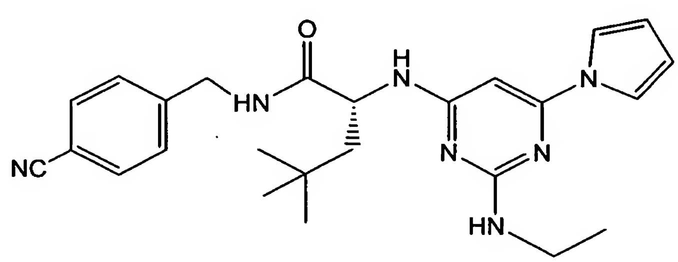
	818697
	005195
	018412
	030876

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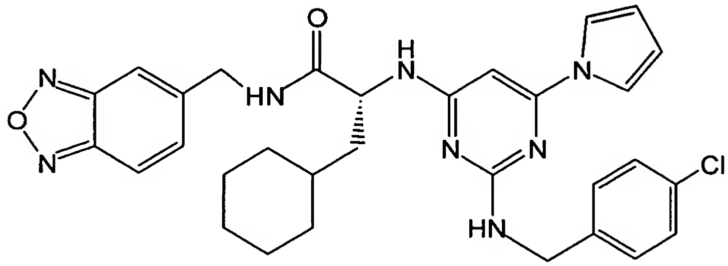
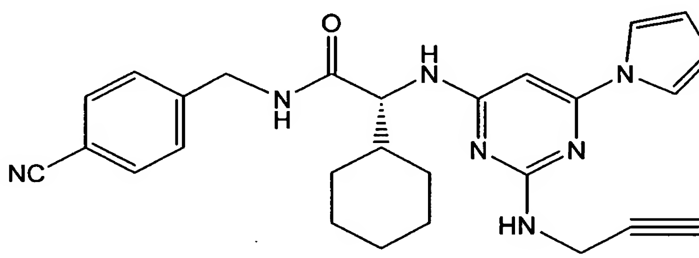
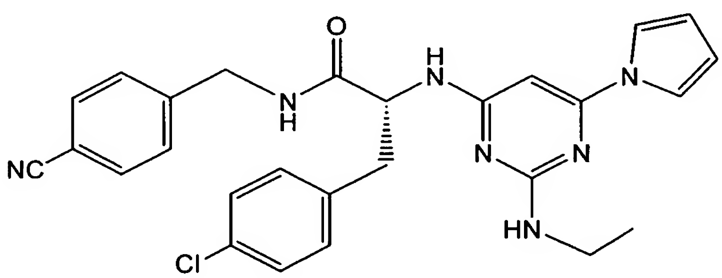
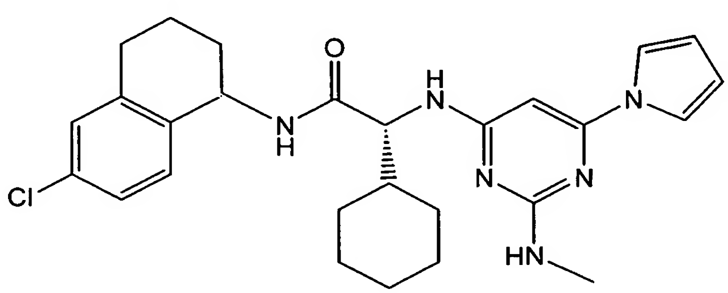
	031155
 054101	
	066361
	095564

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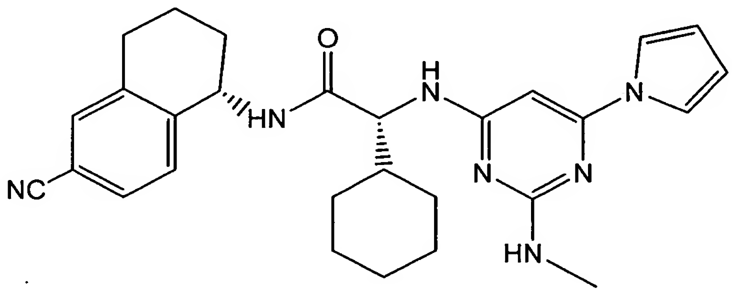
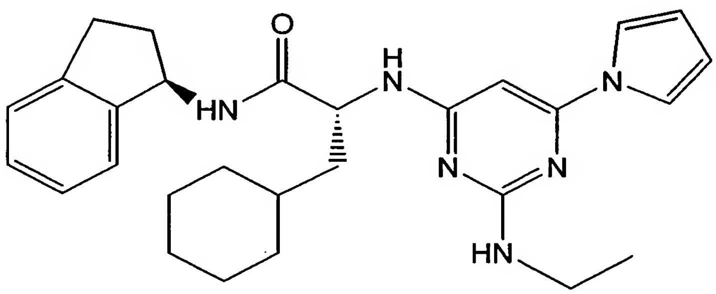
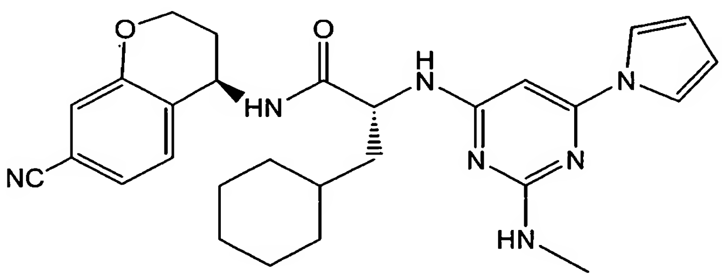
	109718
	129311
	139299

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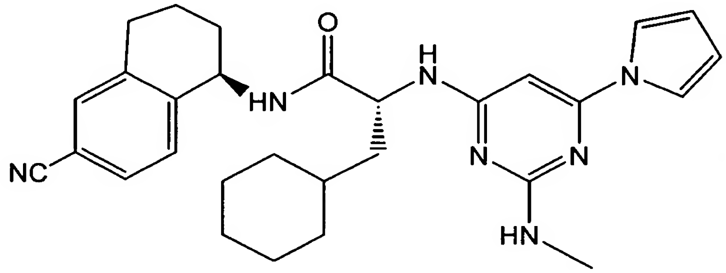
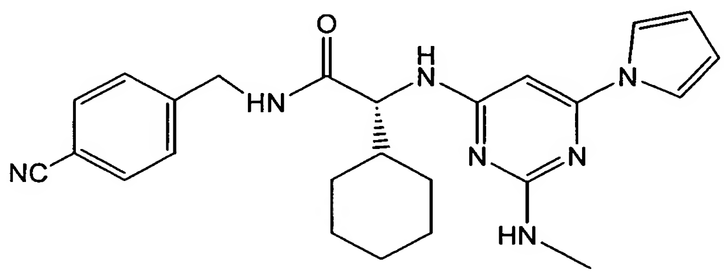
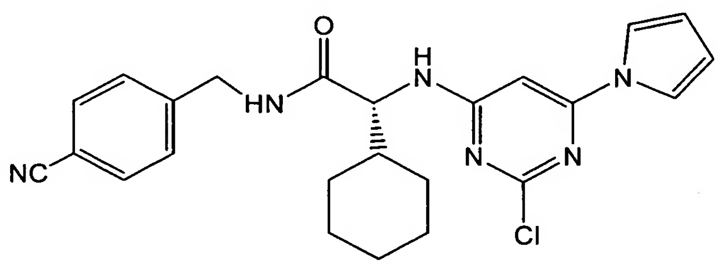
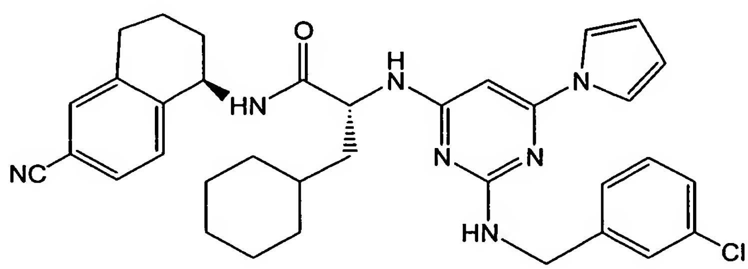
	154213
	167307
	178323
	192258

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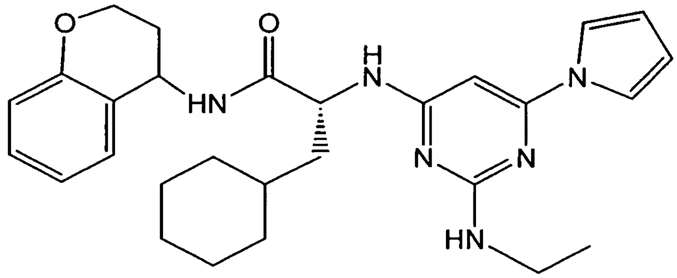
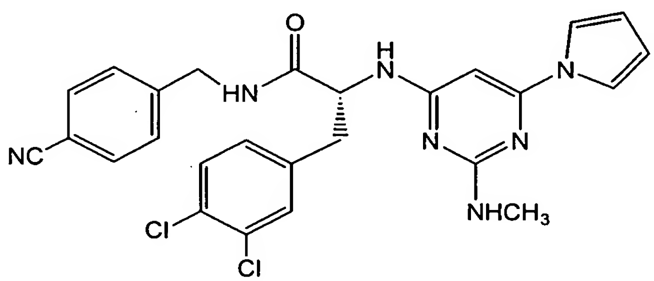
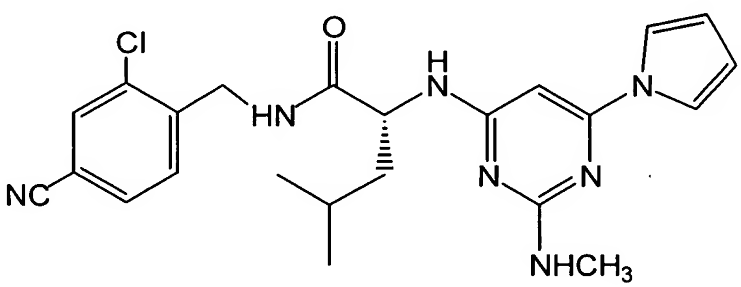
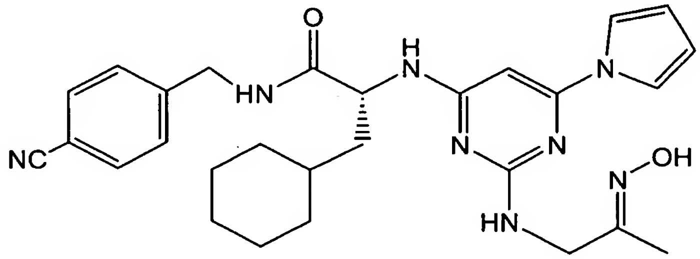
	198950
	215301
	215318
	218245

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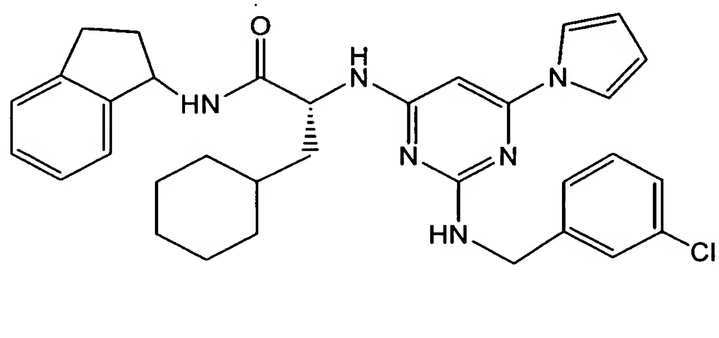
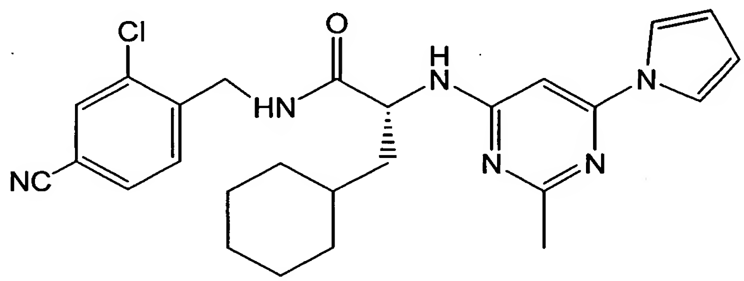
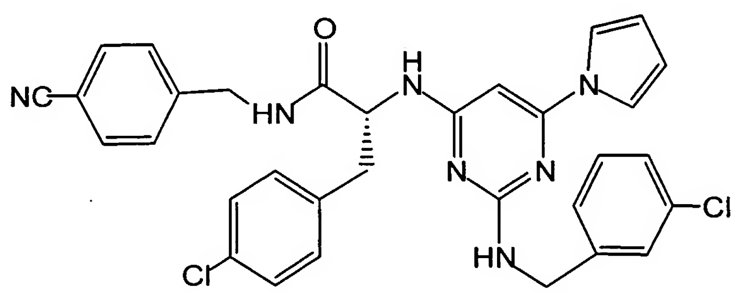
	222477
	237360
	307742

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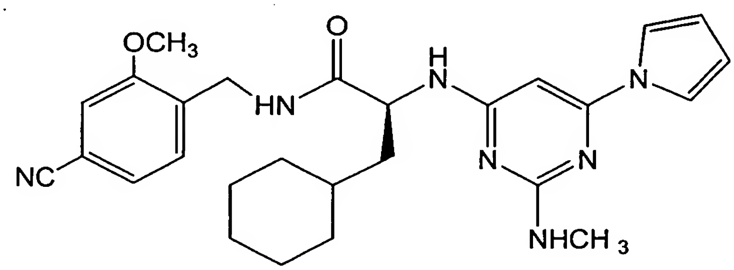
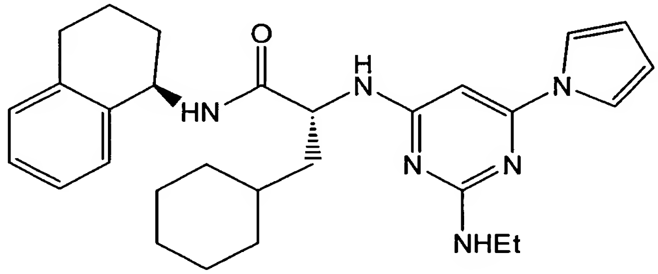
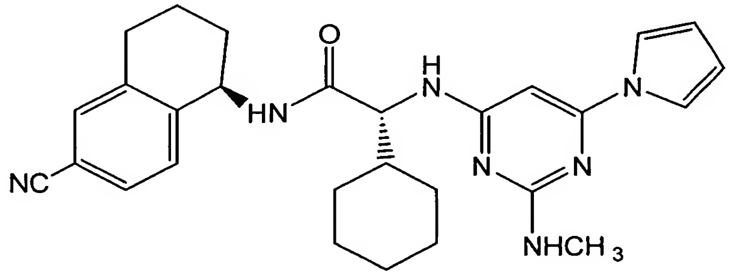
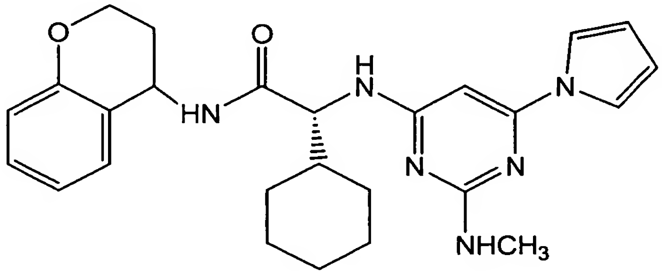
	309001
	312972
	327891
	334878

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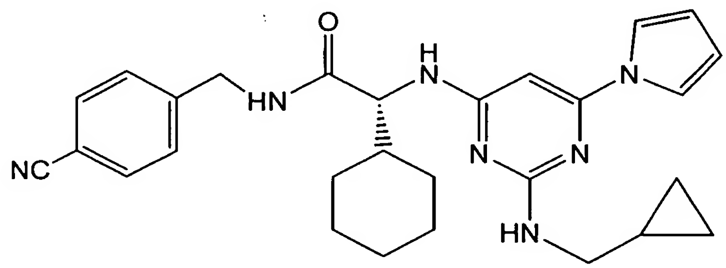
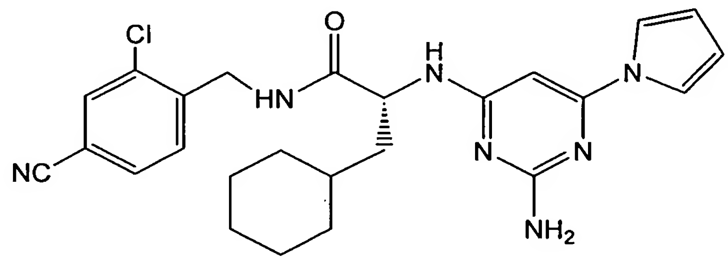
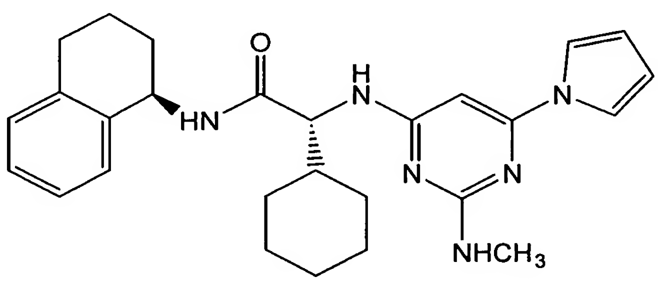
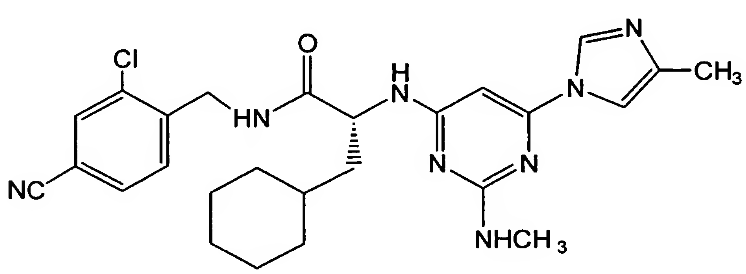
	337854
	347952
	360912
	368057

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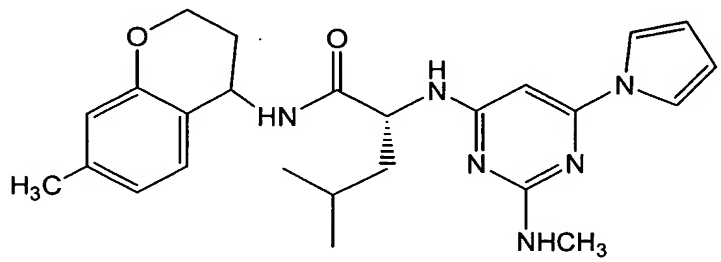
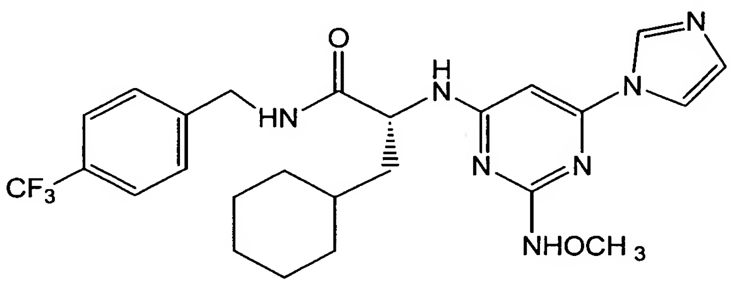
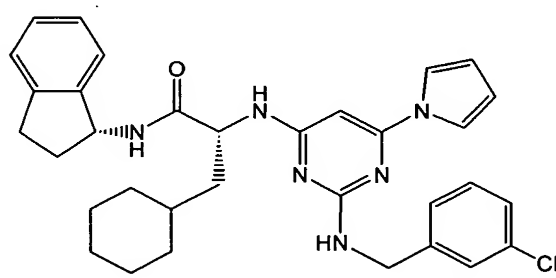
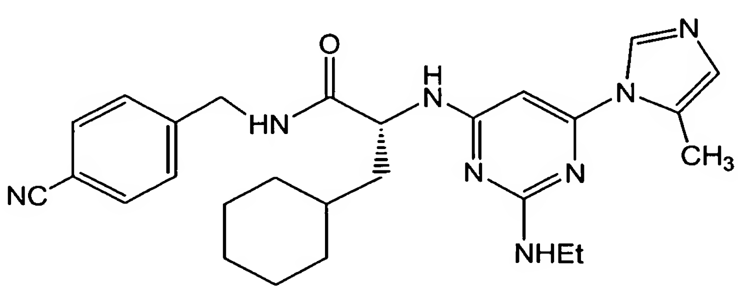
	380712
	395117
	410204
	412904

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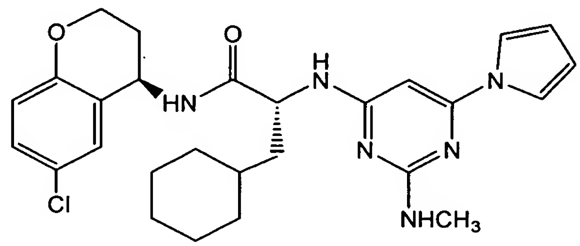
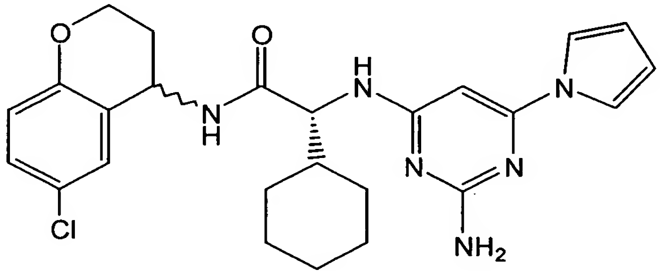
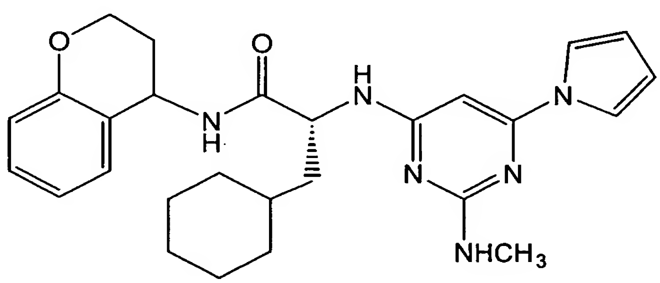
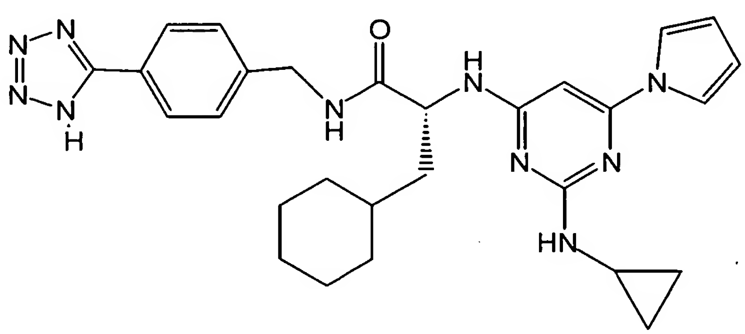
	414904
	424569
	426754
	442350

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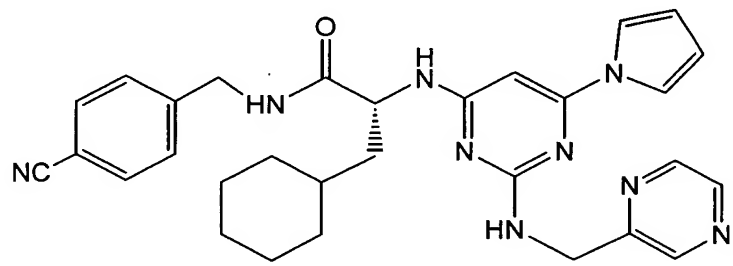
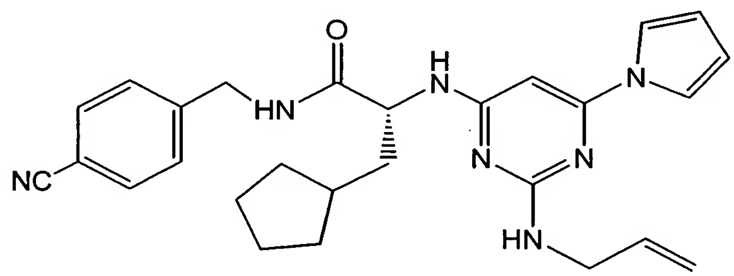
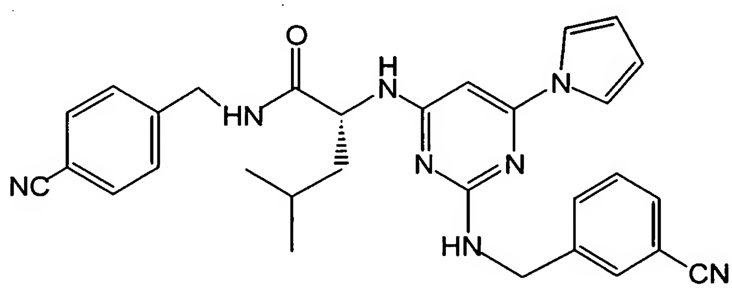
	444713
	452881
	456816

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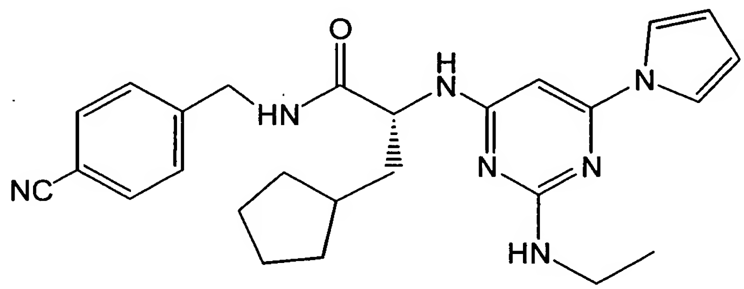
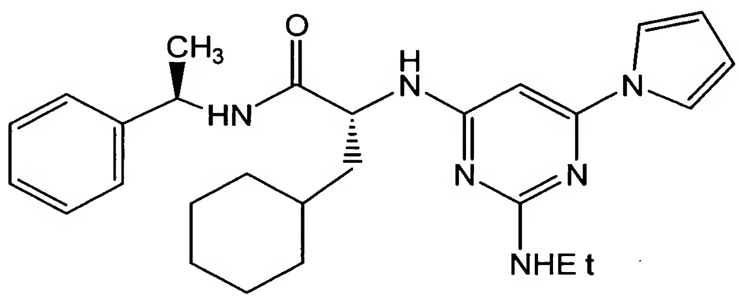
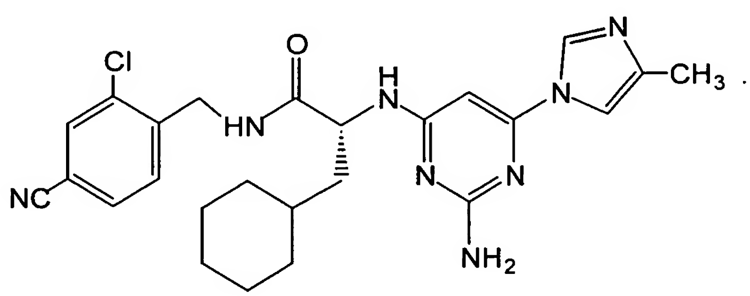
	466502
	492190
	512937

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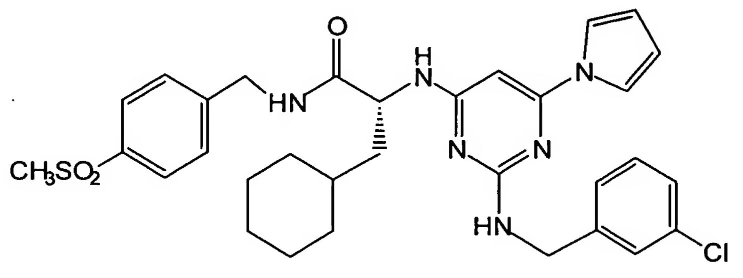
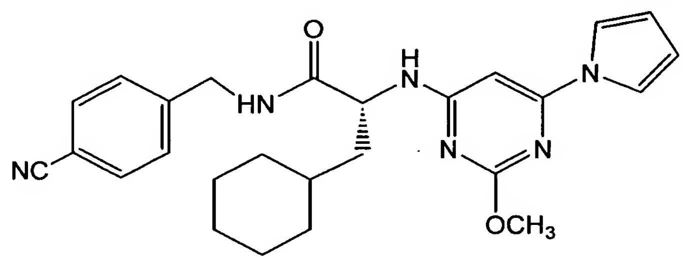
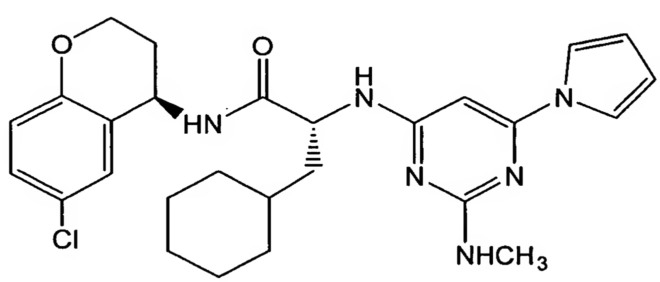
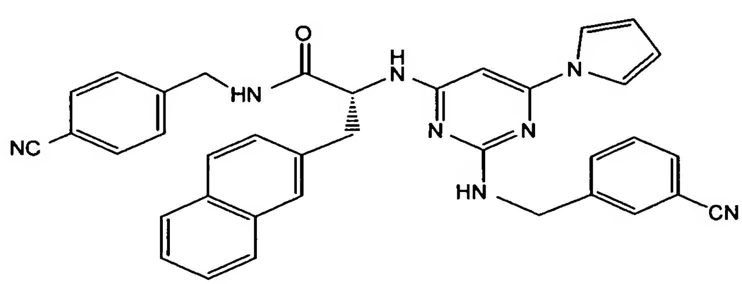
	556200
	447846
	572620
	588712

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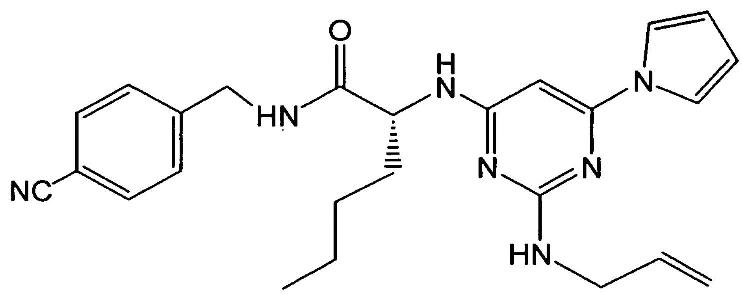
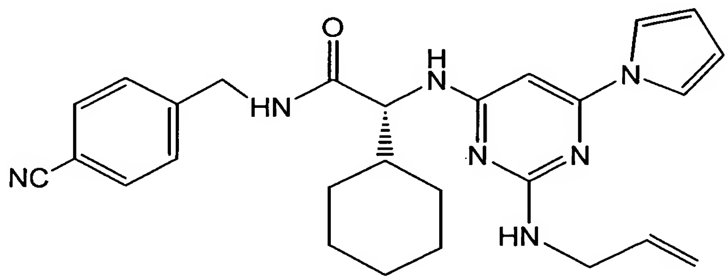
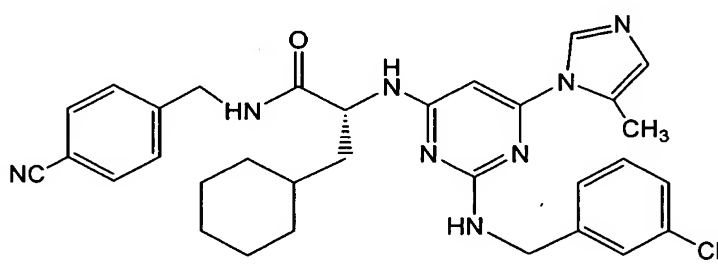
	596982
	603364
	662666

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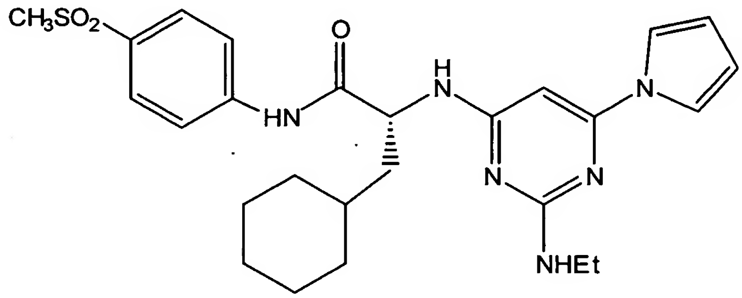
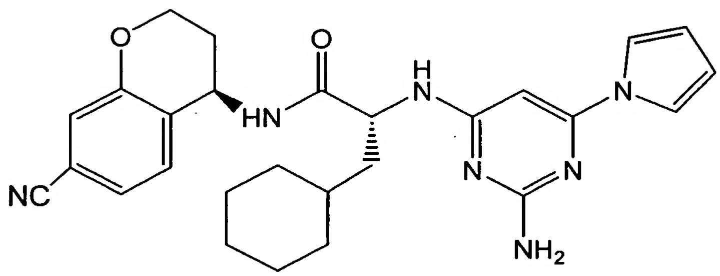
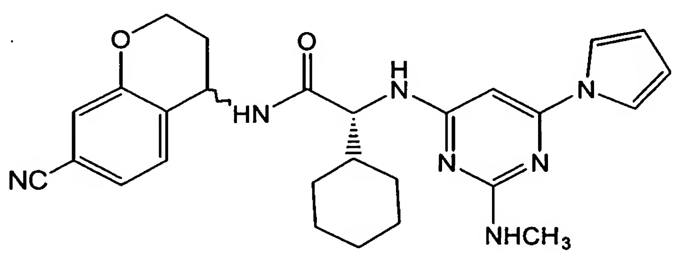
	670583
	698545
	708752

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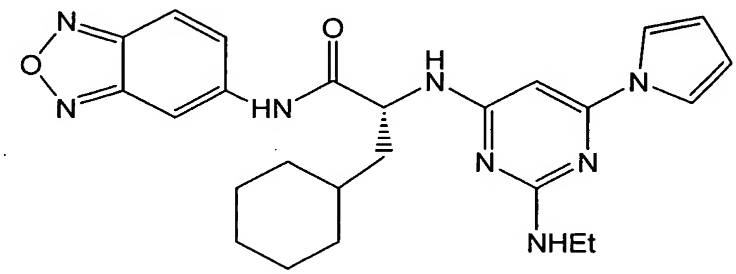
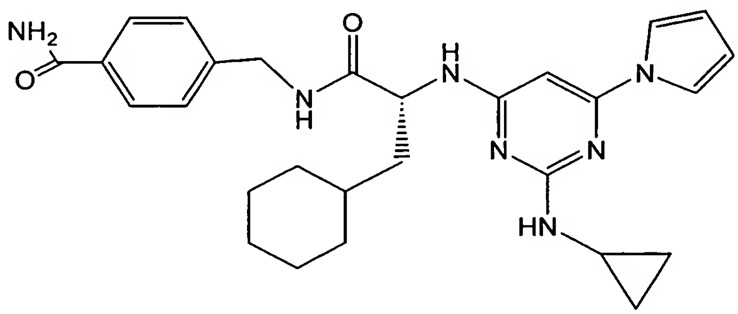
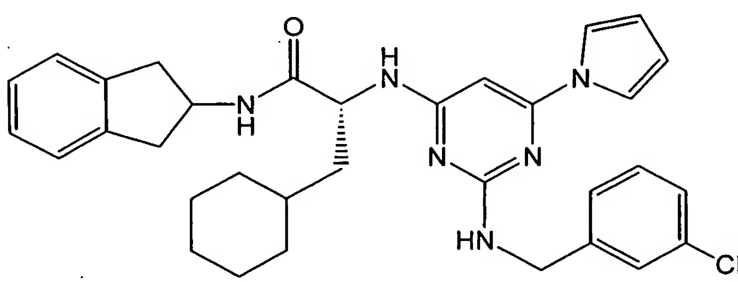
	724612
	739750
	797241

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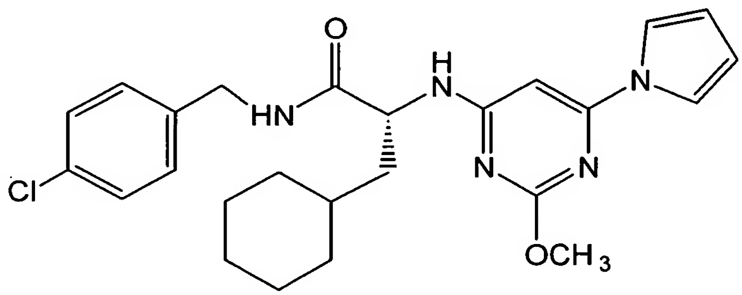
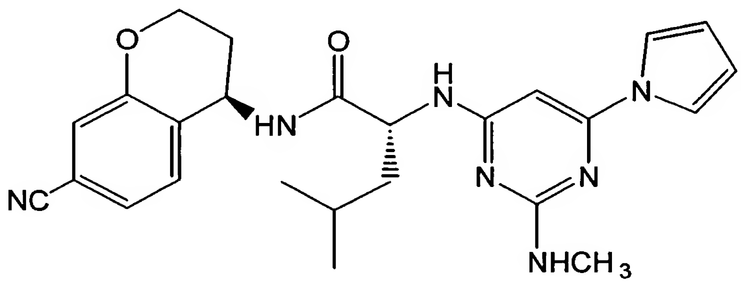
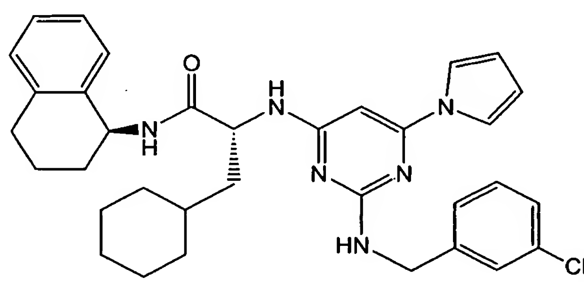
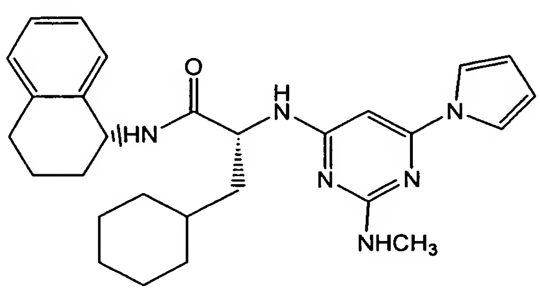
	817552
	824754
	835714
	847939

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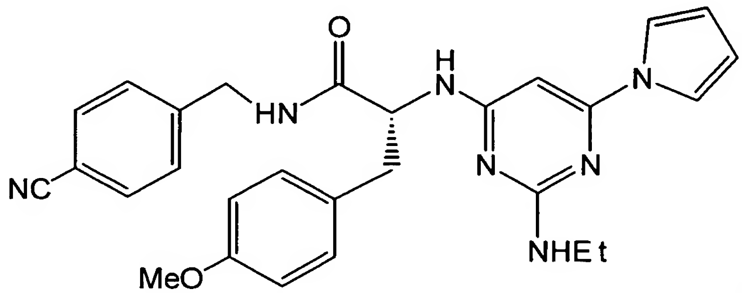
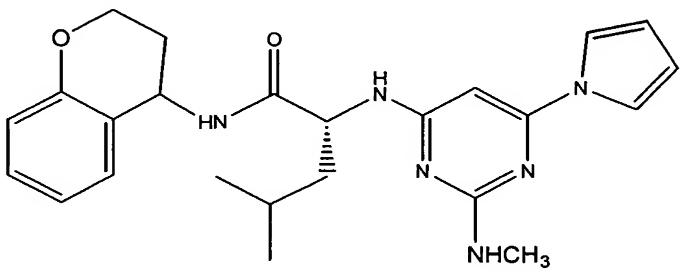
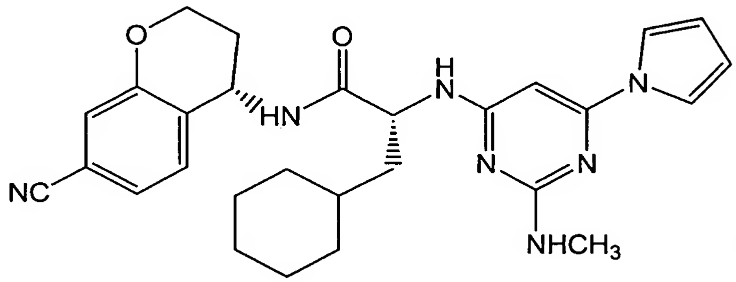
	859657
	881196
	919420

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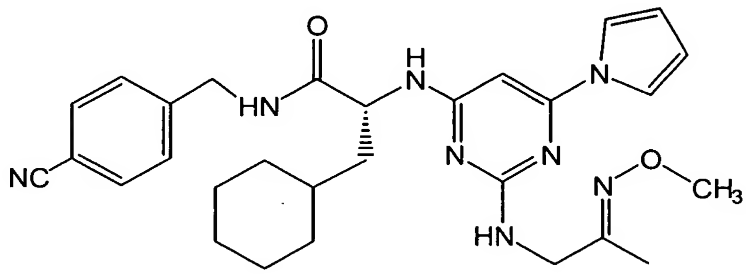
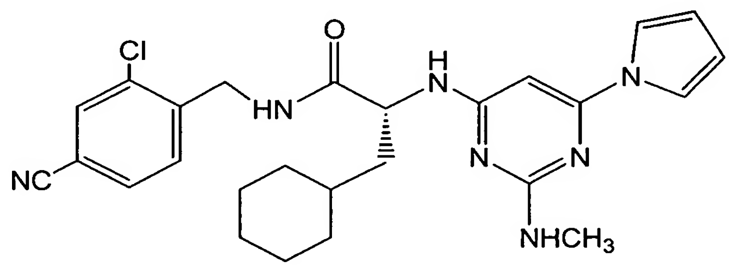
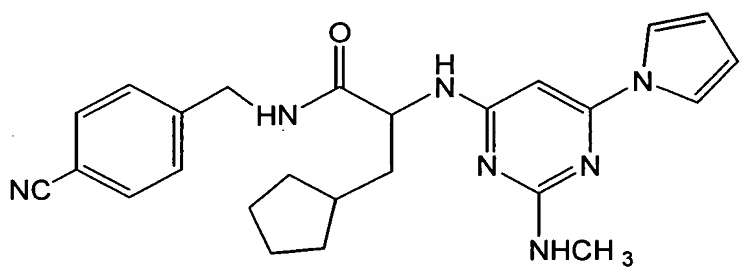
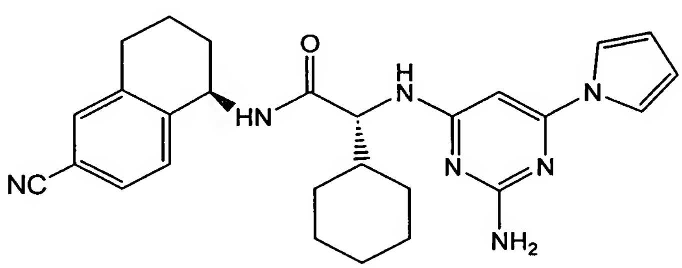
	936852
	960142
	968882
	993416

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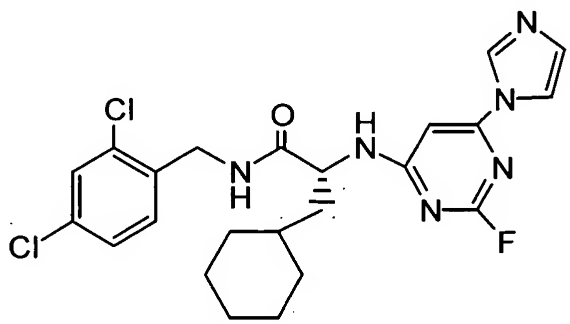
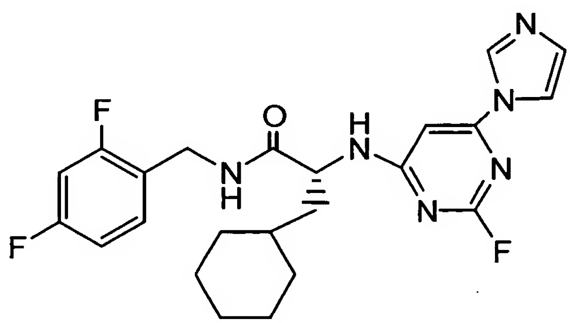
	339883
	428825

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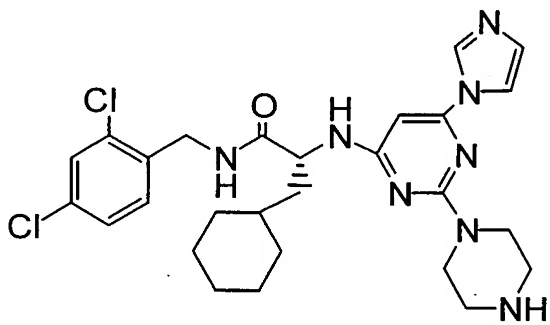
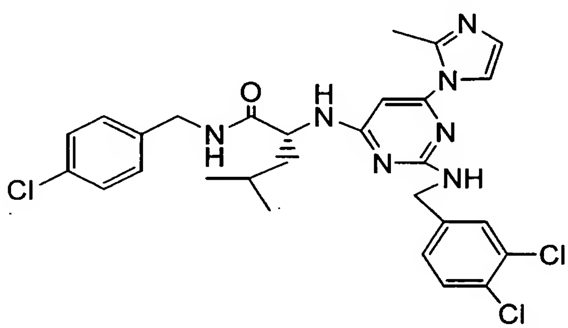
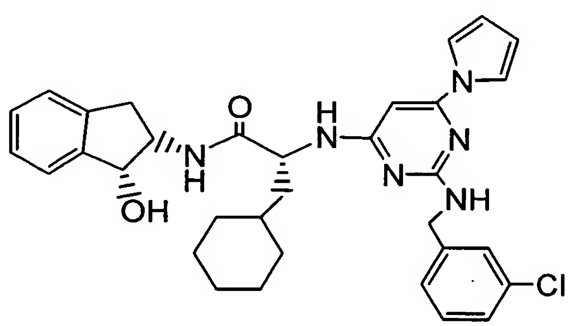
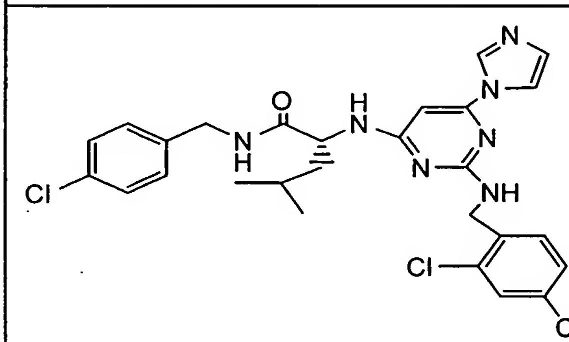
	459868
	397897
	703779
	966132

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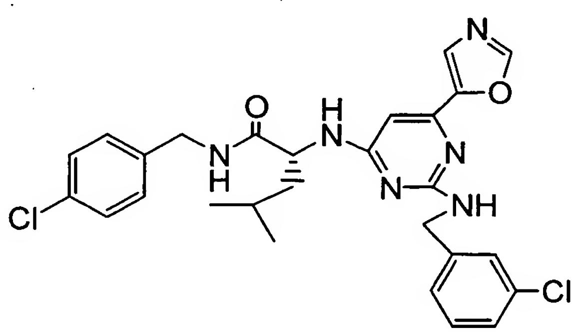
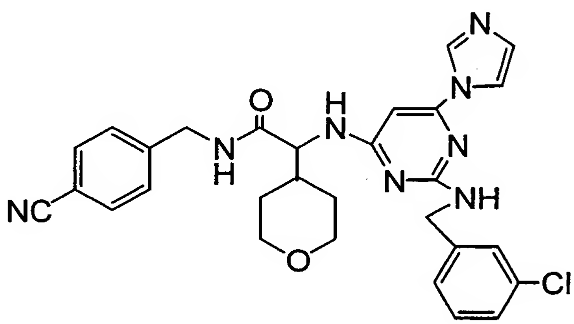
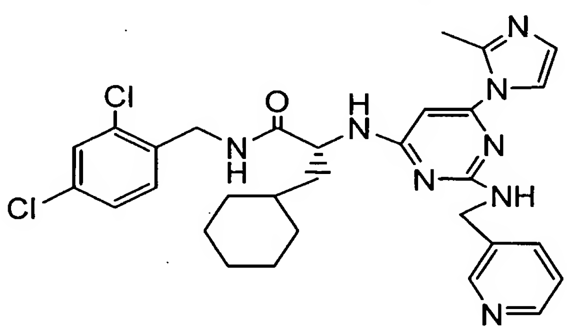
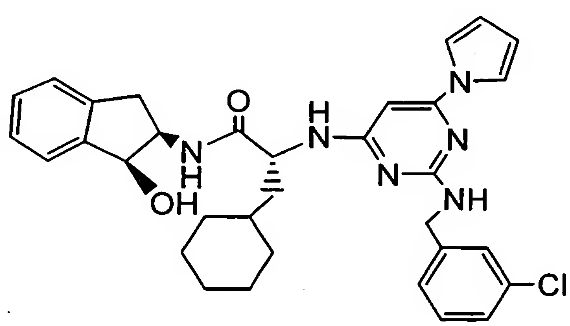
	276572
	748623
	770799
	474269

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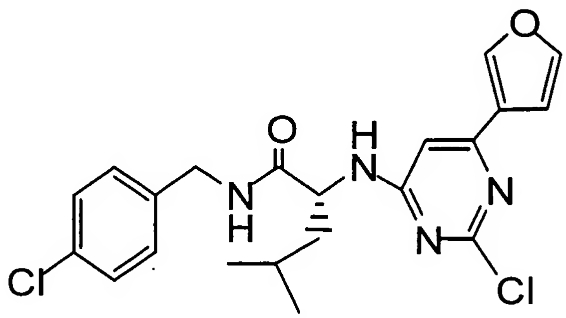
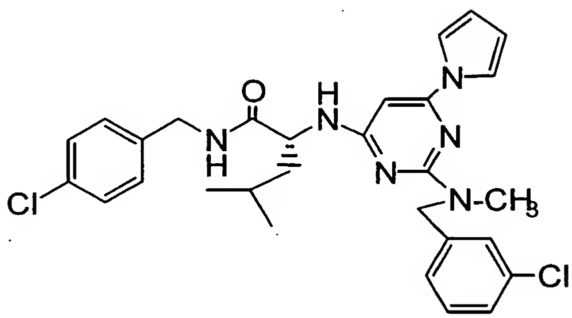
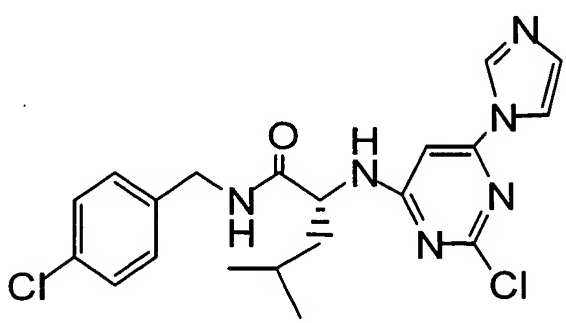
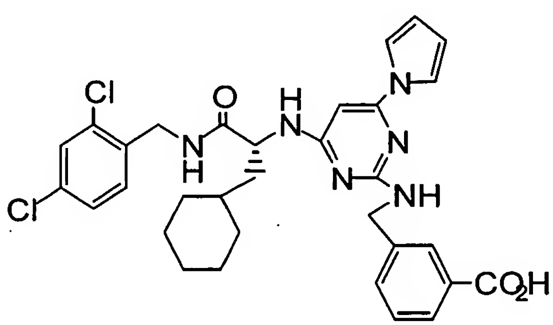
	715066
	884607
	387845
	334057

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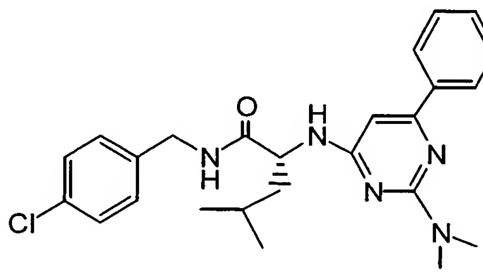
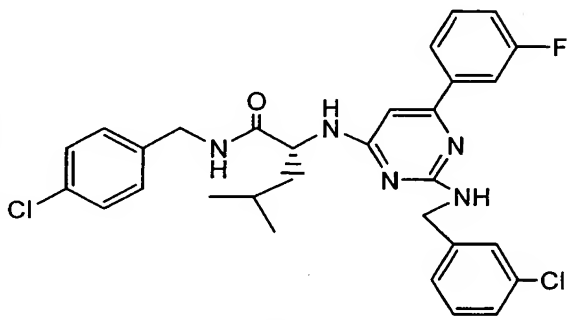
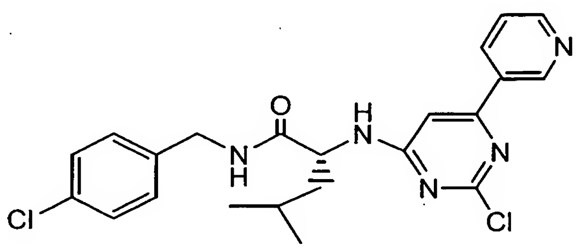
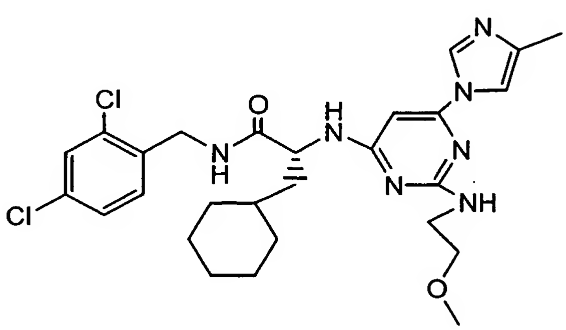
	703736
	169968
	405907
	577561

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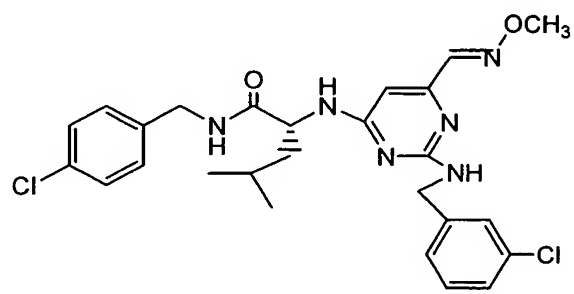
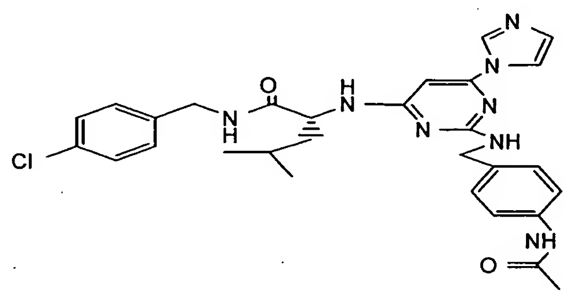
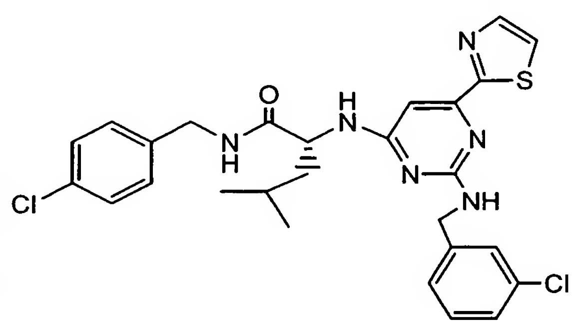
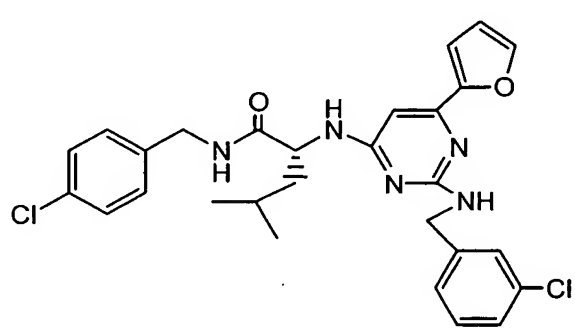
	651408
	834615
	836641
	419551

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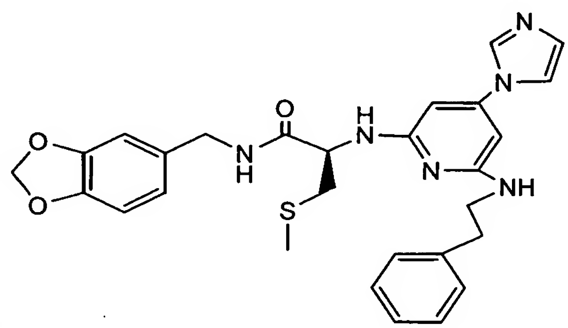
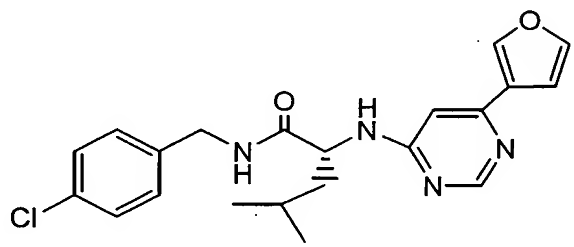
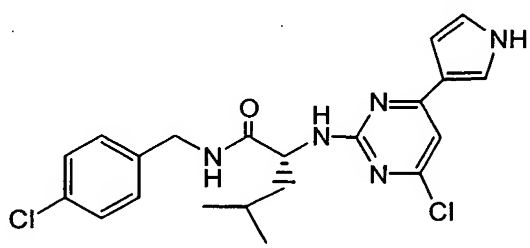
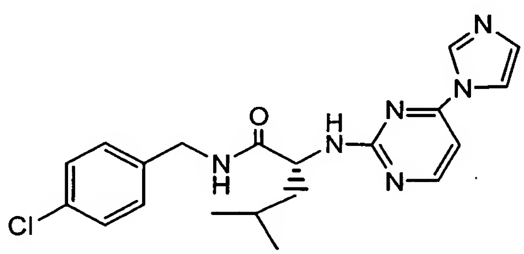
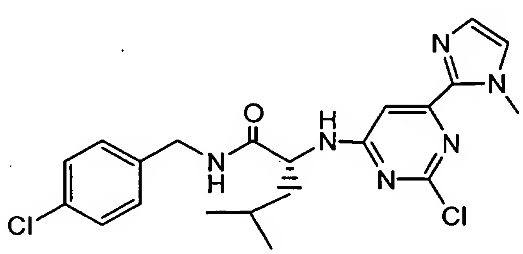
	830601
	555804
	031557
	085311
	340085

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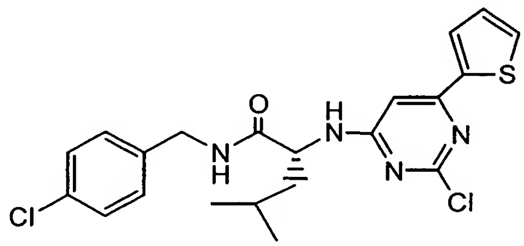
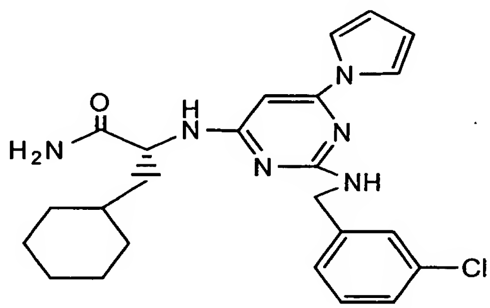
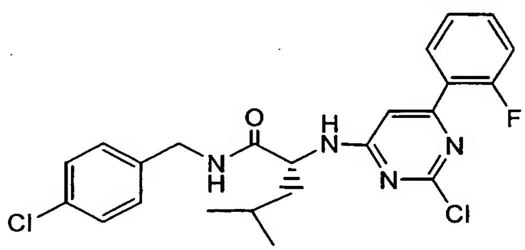
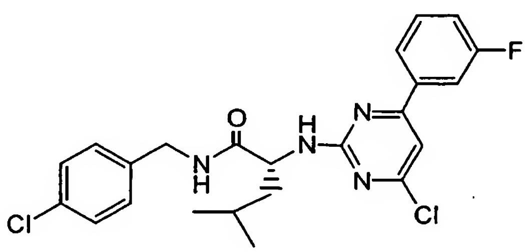
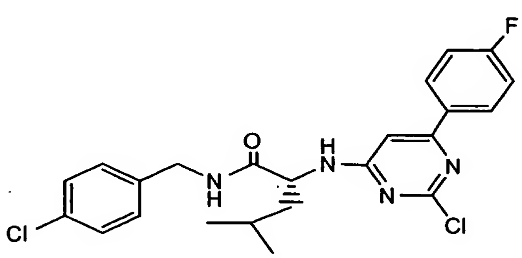
	574878
	906426
	396104
	404682
	637763

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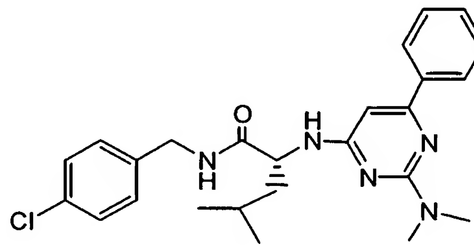
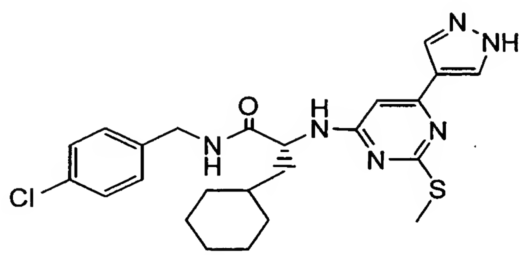
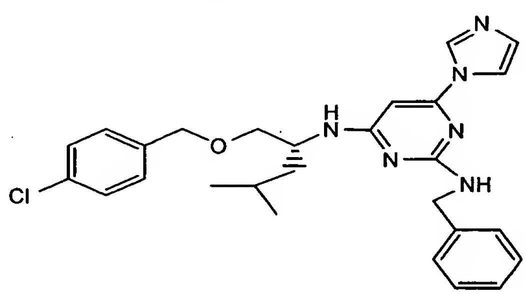
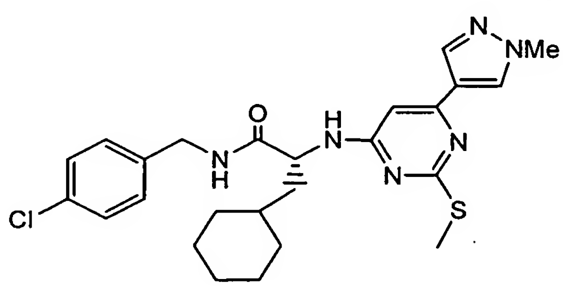
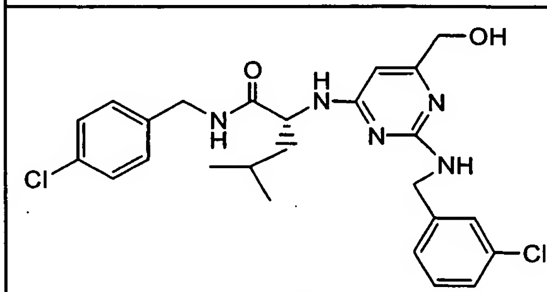
	006801
	309888
	889134
	888340
	407599

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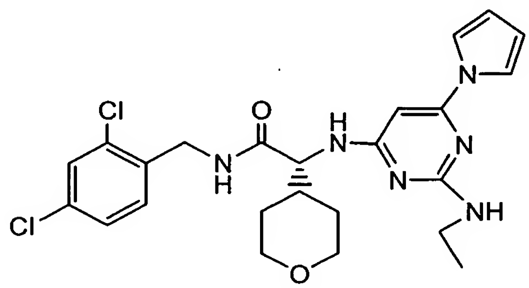
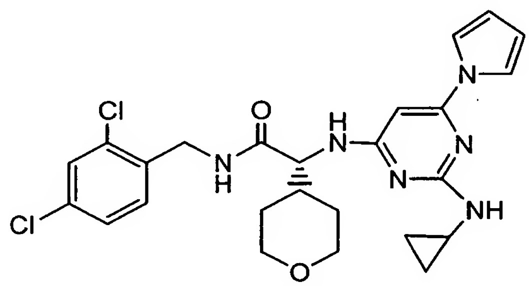
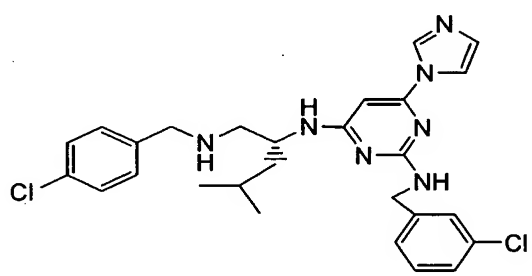
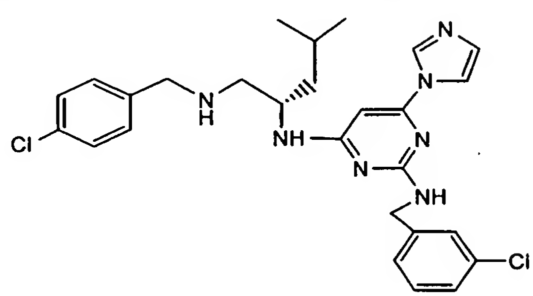
	458001
	214357
	324675
	622414

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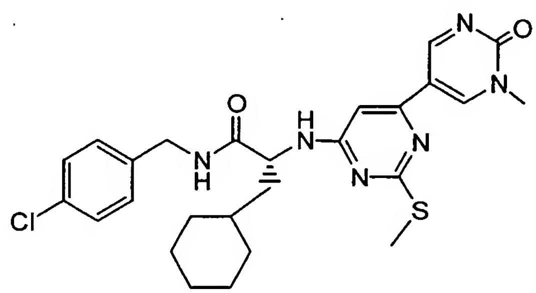
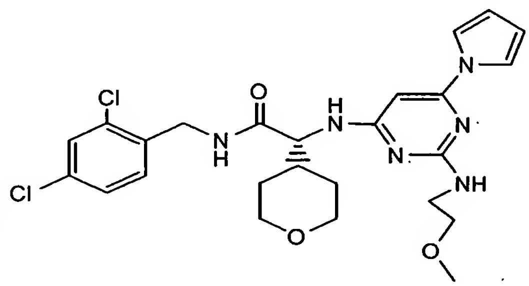
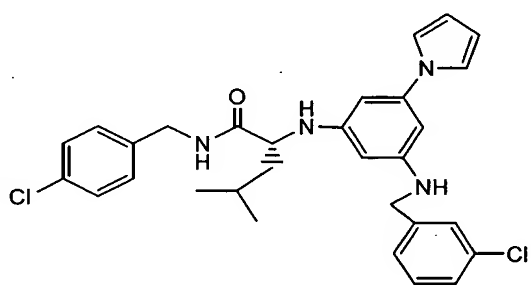
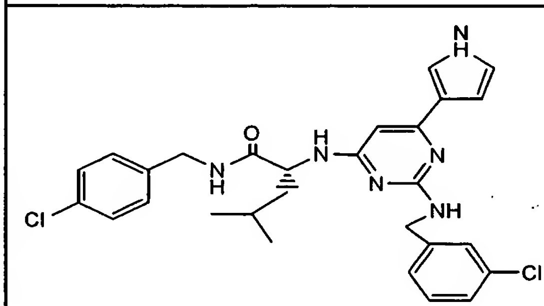
	193177
	979425
	054066
	170440

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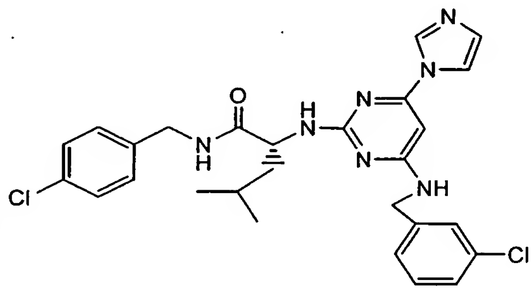
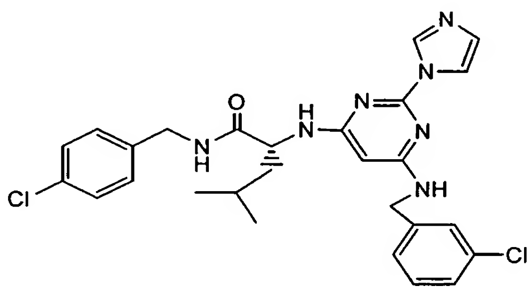
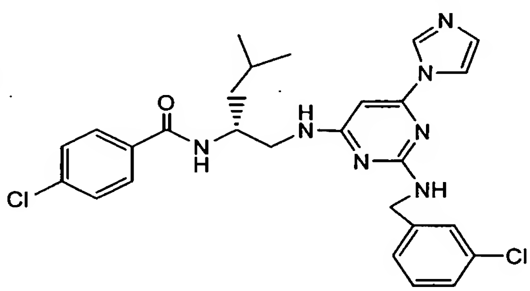
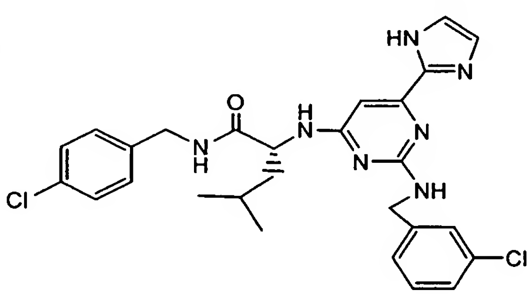
	129647
	327168
	600629
	984213

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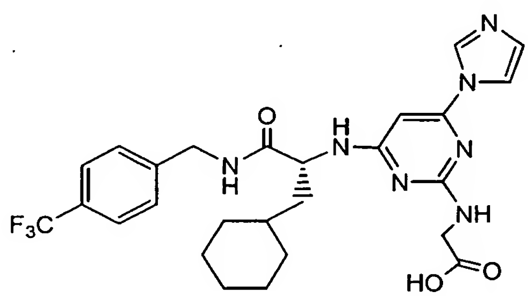
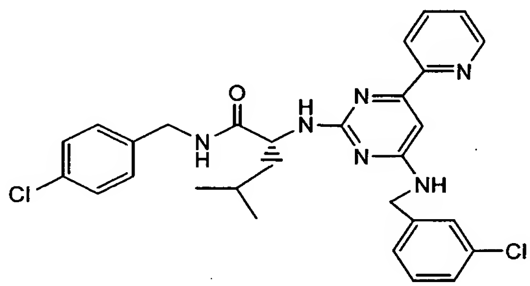
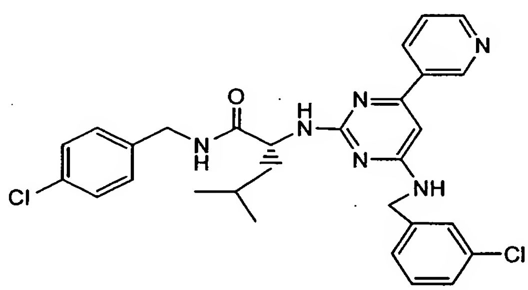
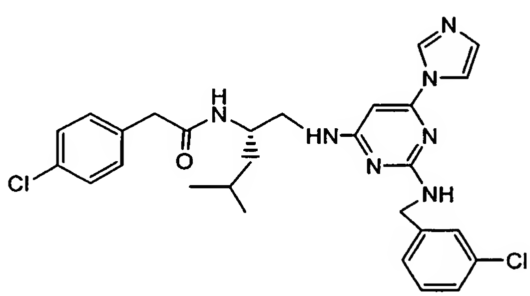
	832914
	065864
	727448
	429933

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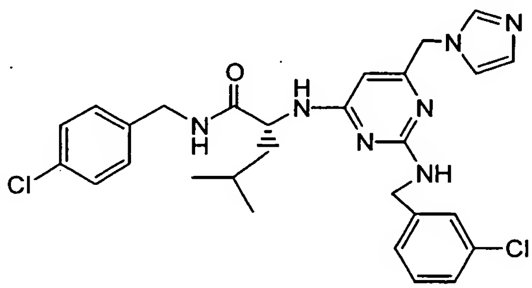
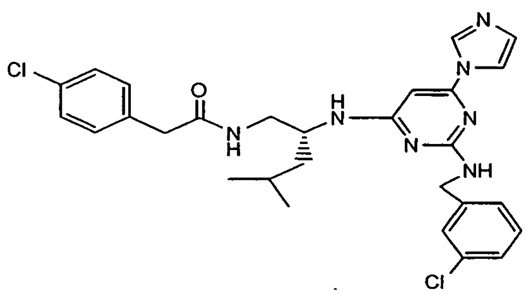
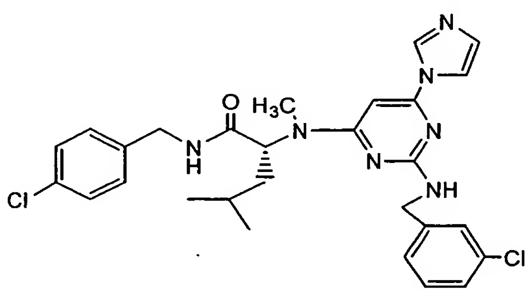
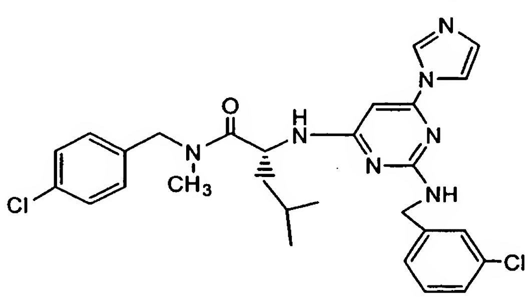
	603335
	826751
	844156
	930501

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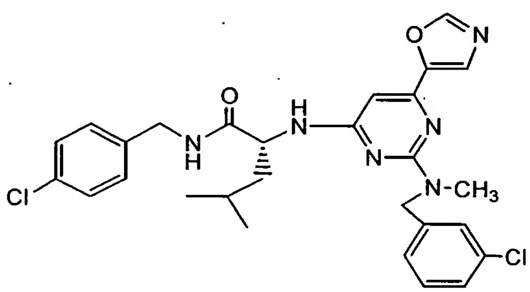
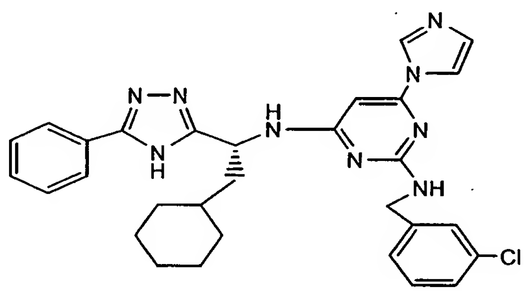
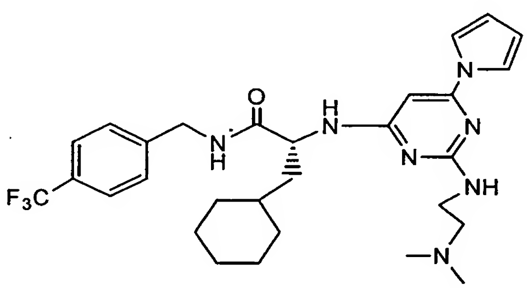
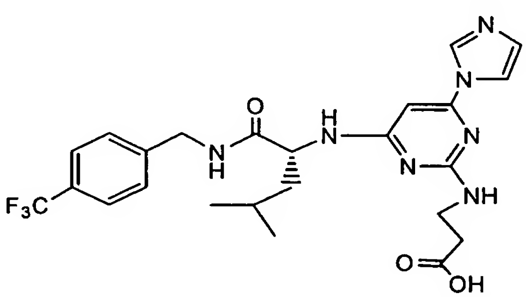
	963106
	583734
	059809
	916267

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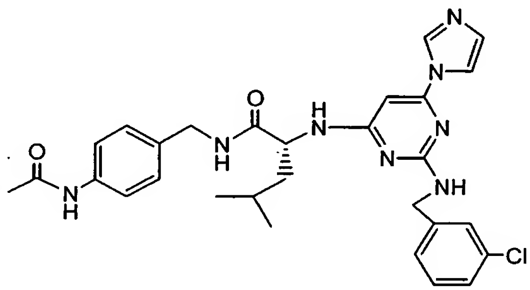
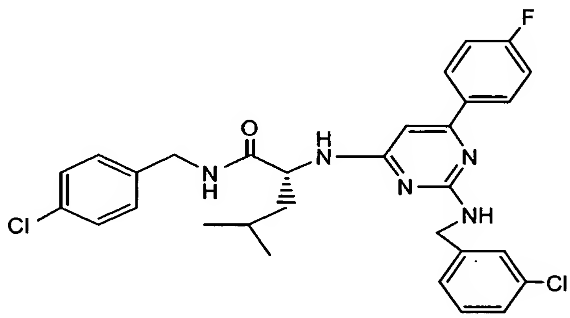
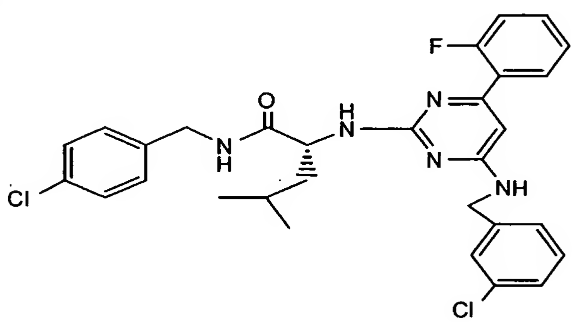
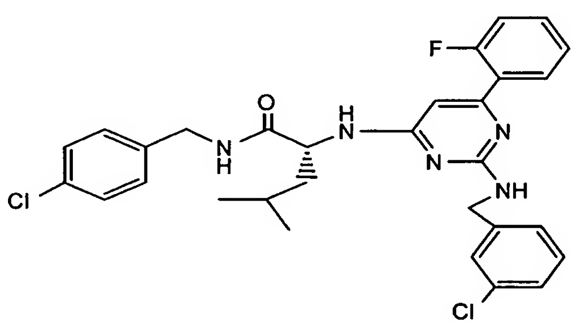
	295459
	386842
	855317
	862111

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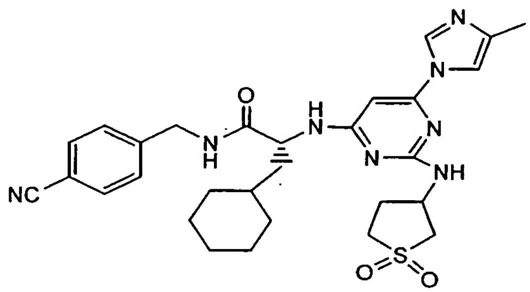
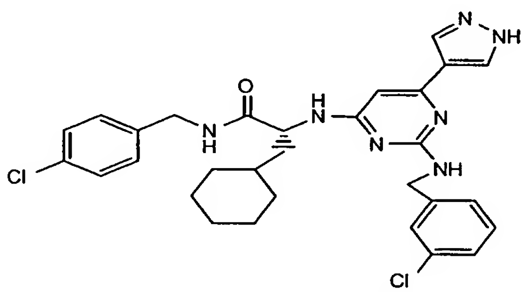
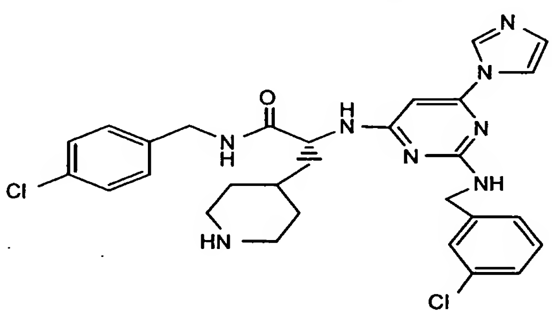
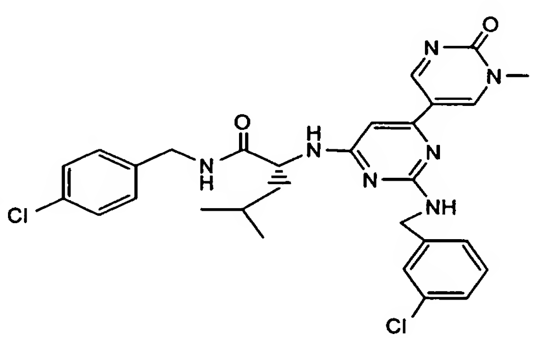
	156360
	808880
	980203
	726338

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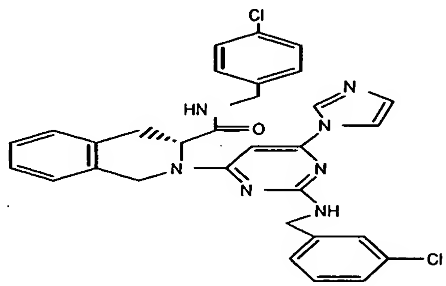
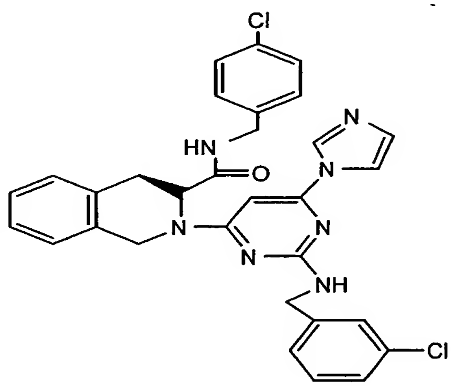
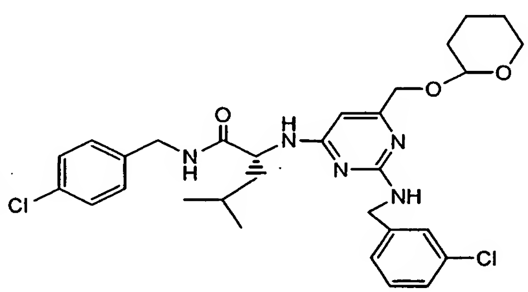
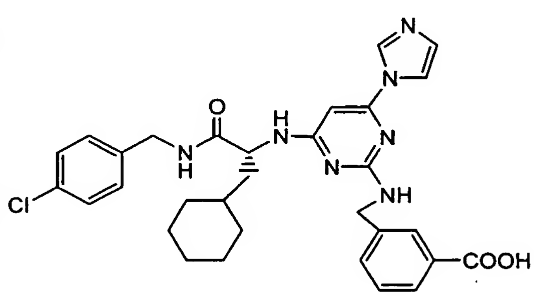
	257040
	327989
	864091
	630878

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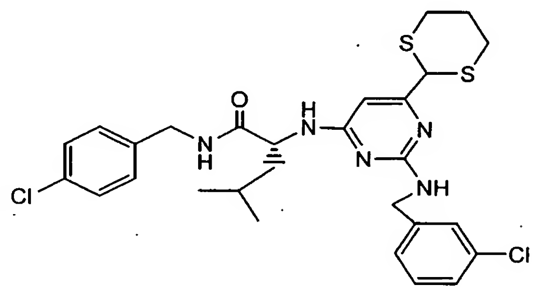
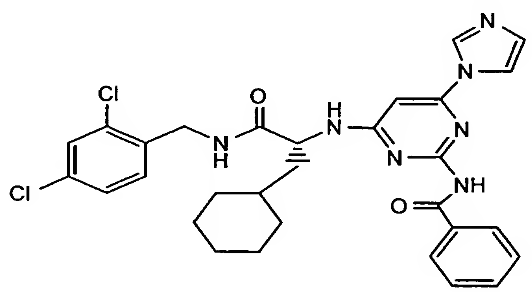
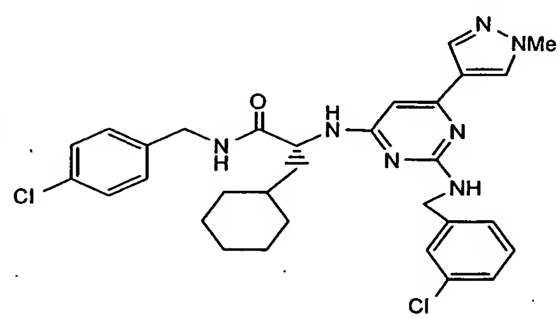
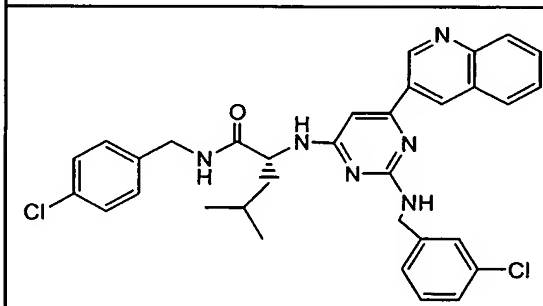
	040296
	027665
	212579
	557004

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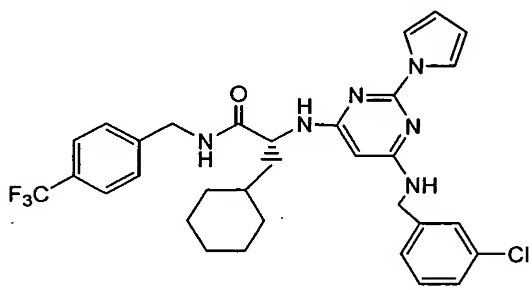
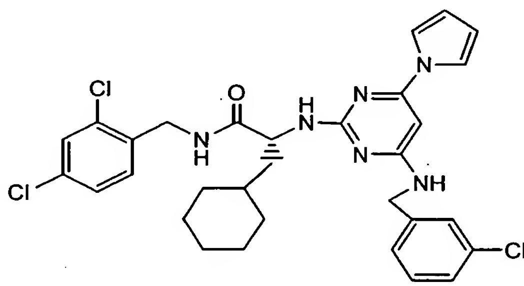
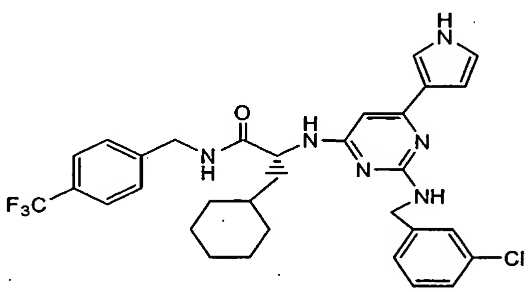
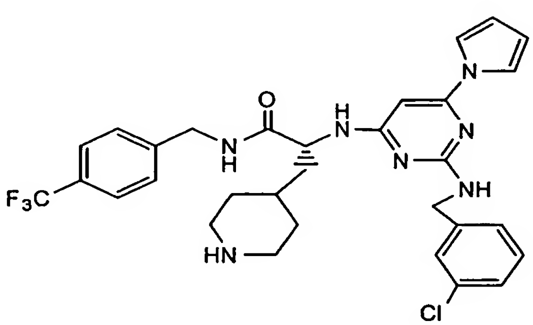
	263415
	302927
	674216
	034480

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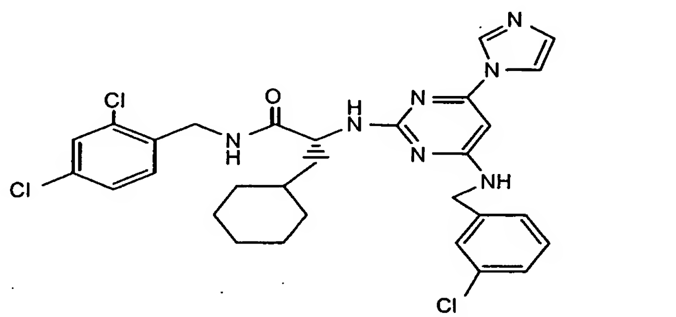
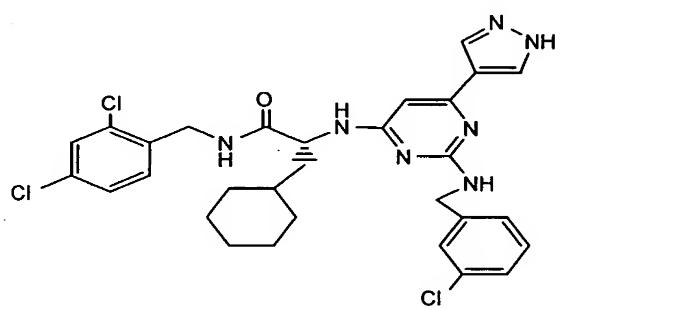
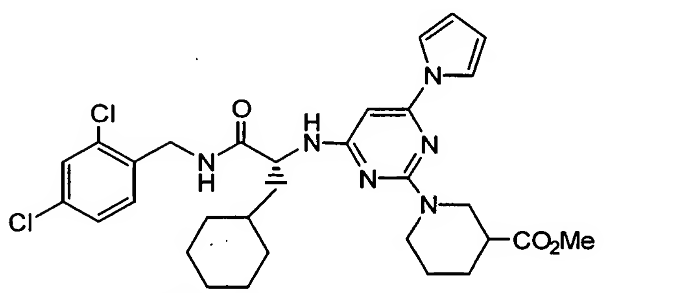
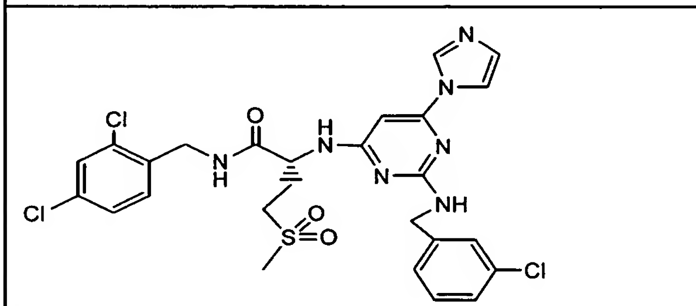
	284784
	390534
	541410
	306344

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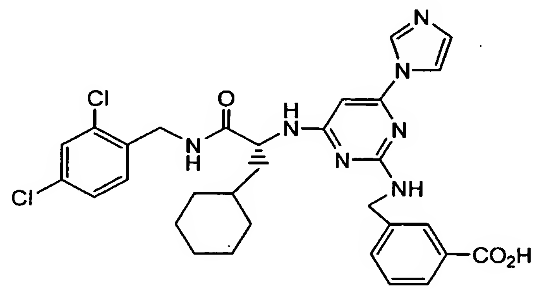
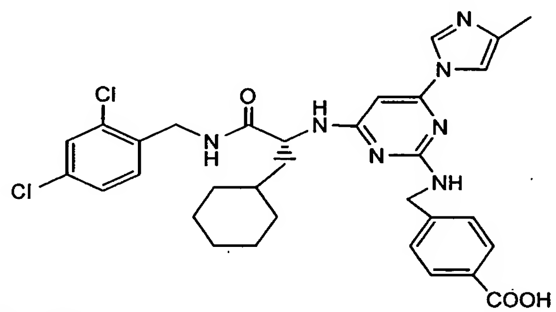
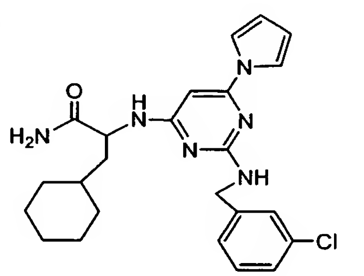
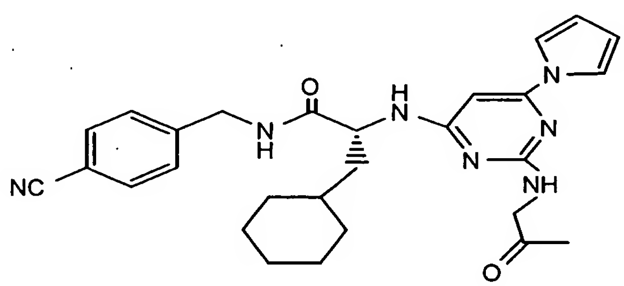
	892732
	209284
	906426
	774868

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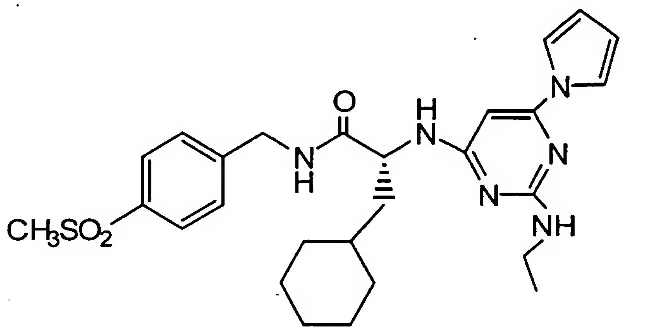
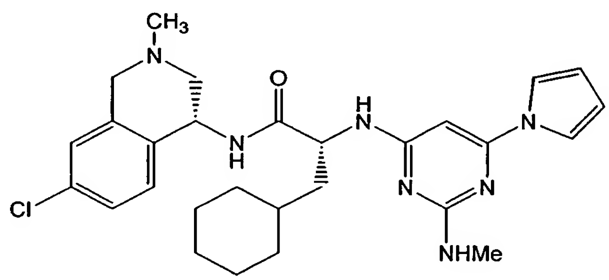
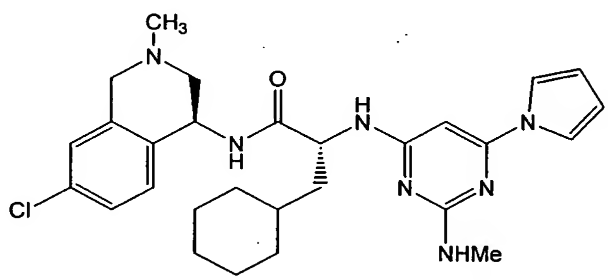
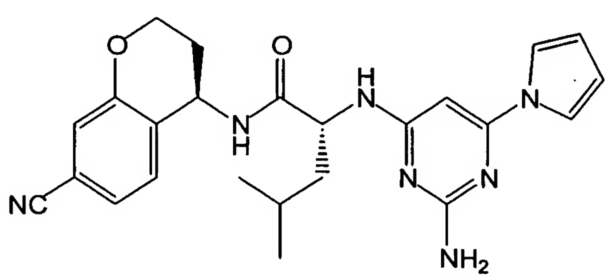
	626899
	367587
	240936
	075438

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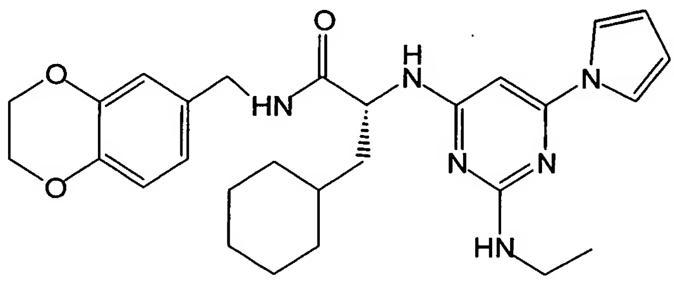
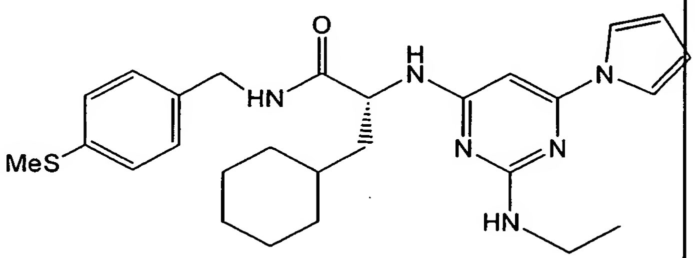
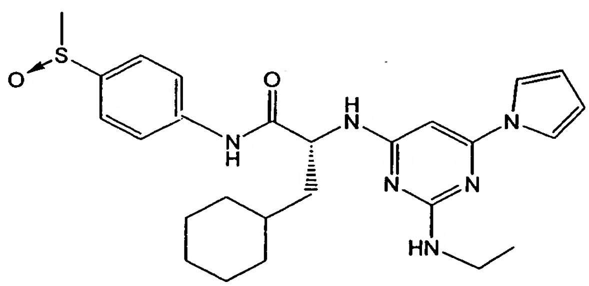
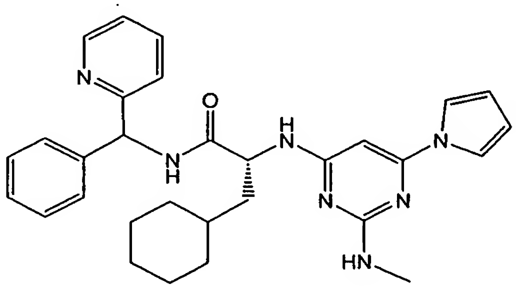
	006518
	026511
	085374
	107571

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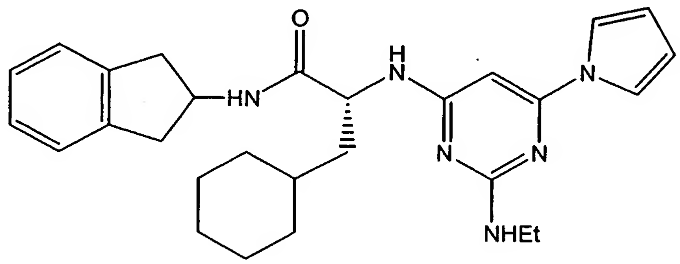
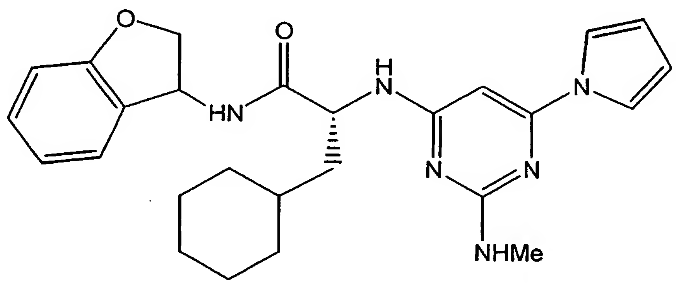
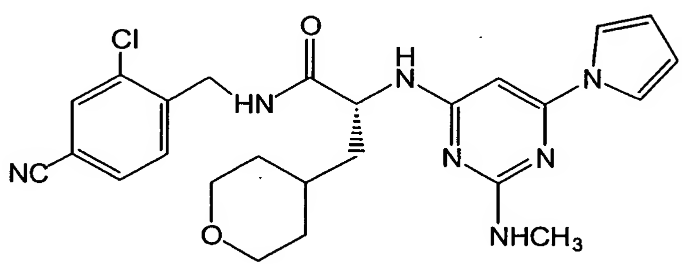
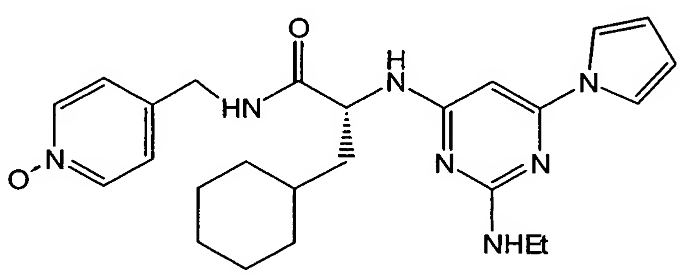
	242518
	25037
	251559
	291582

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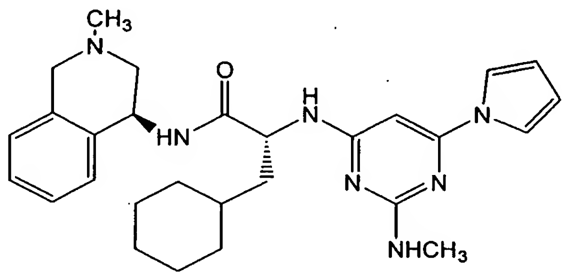
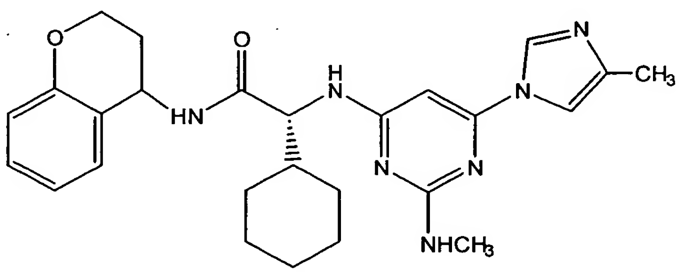
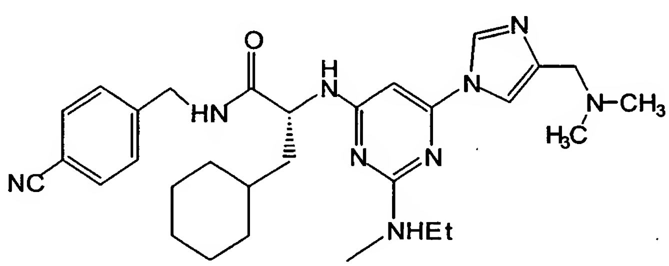
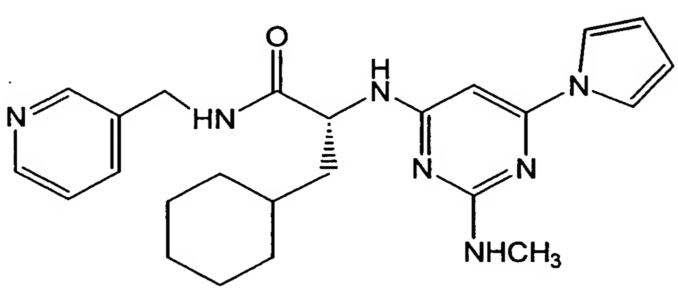
	343424
	357720
	364637
	378606

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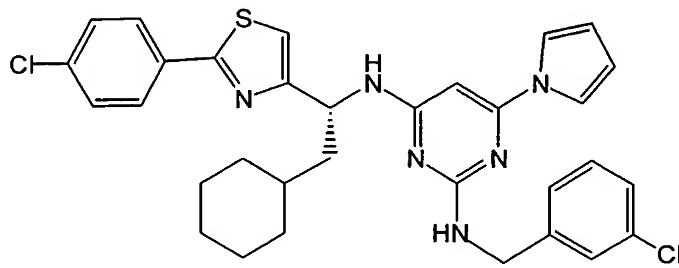
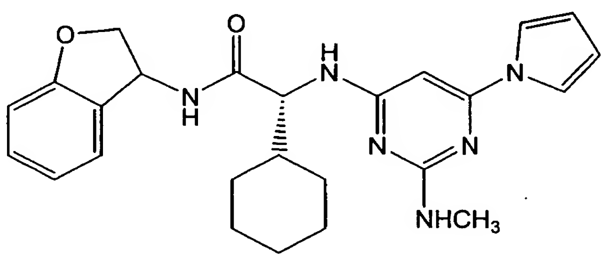
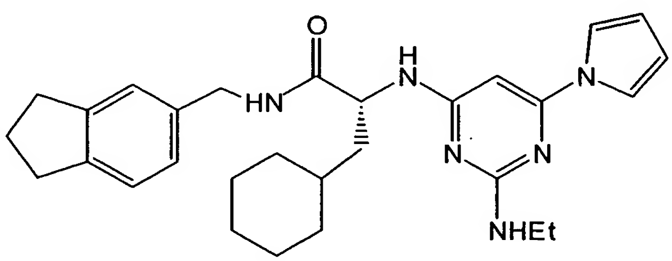
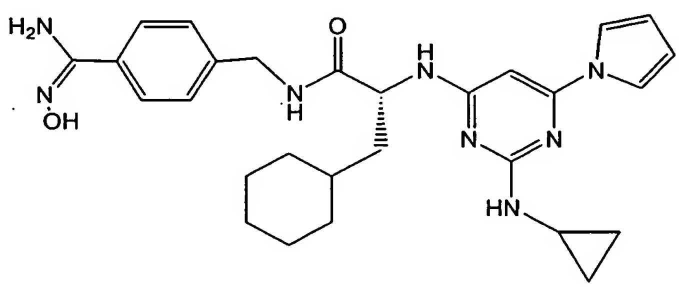
	383670
	567456
	588918
	621206

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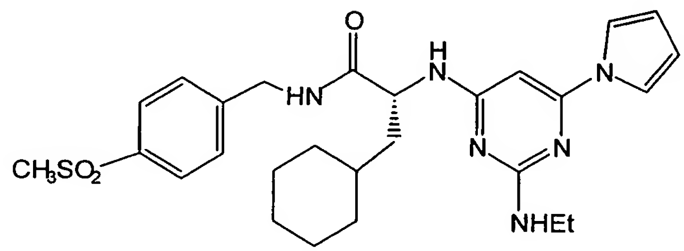
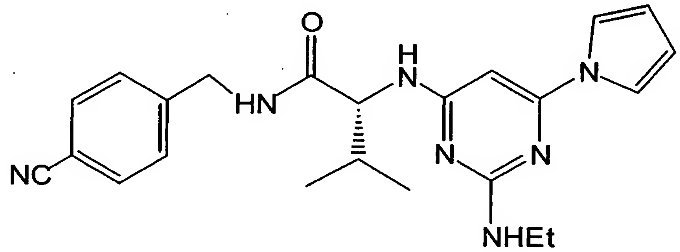
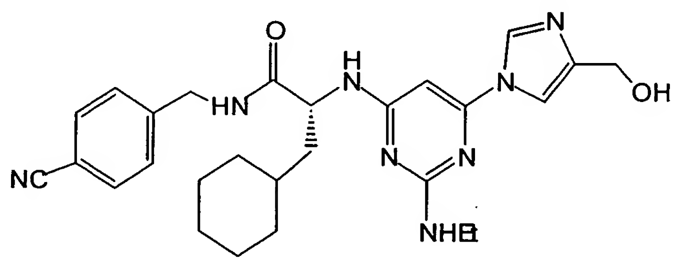
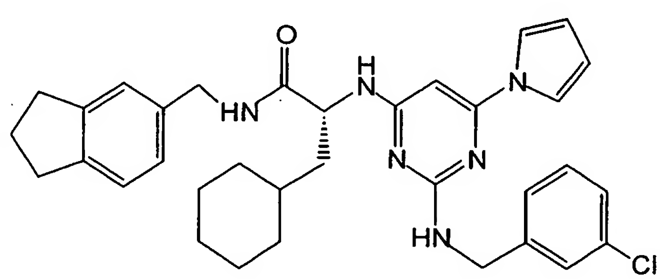
	626899
	629441
	640538
	672975

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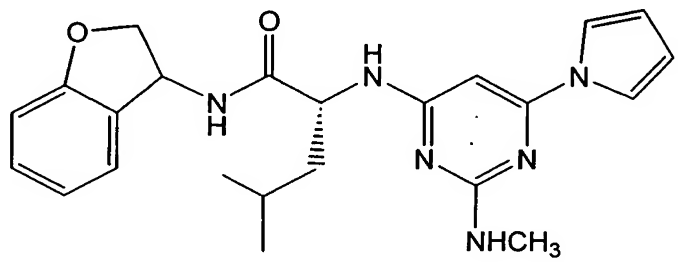
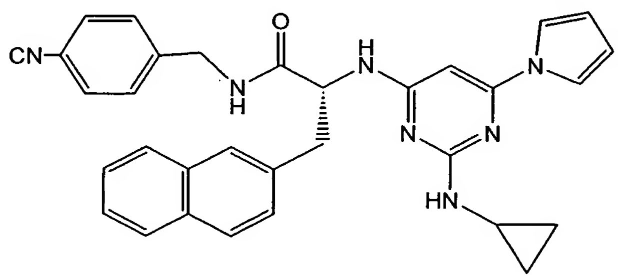
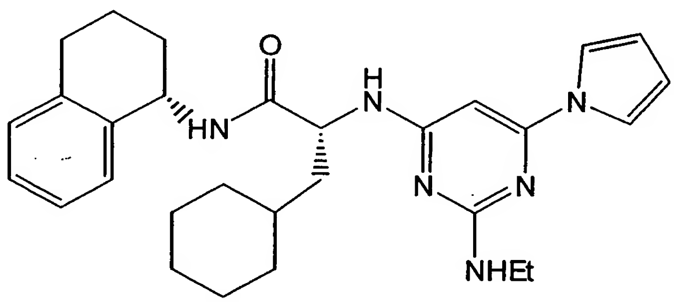
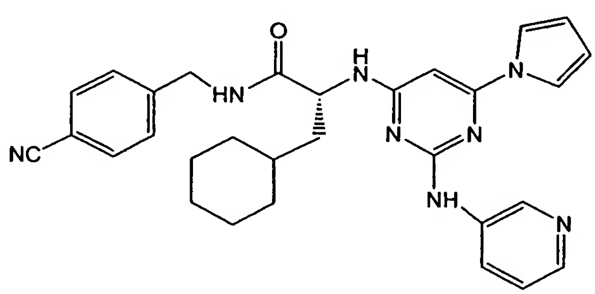
	687899
	709833
	730697
	733184

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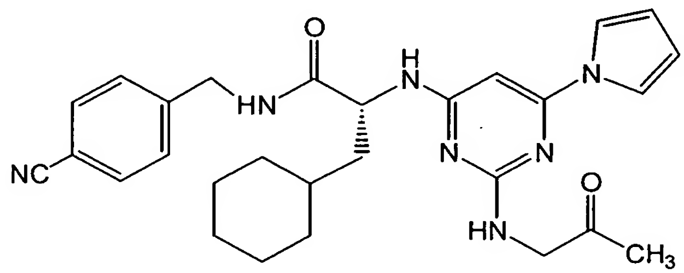
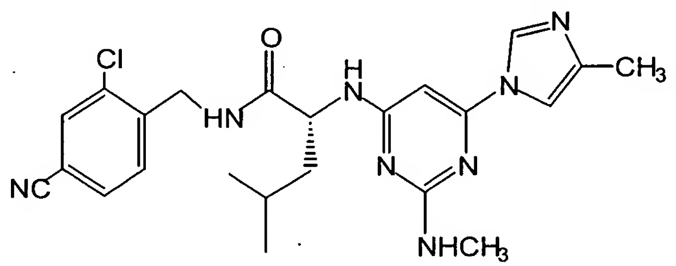
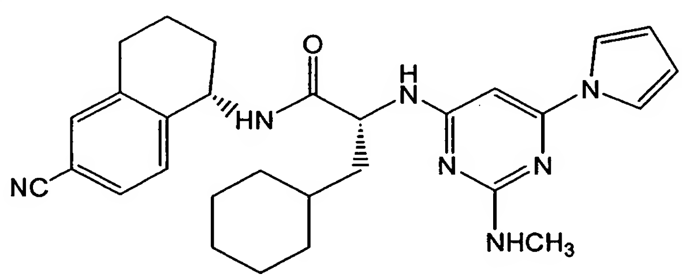
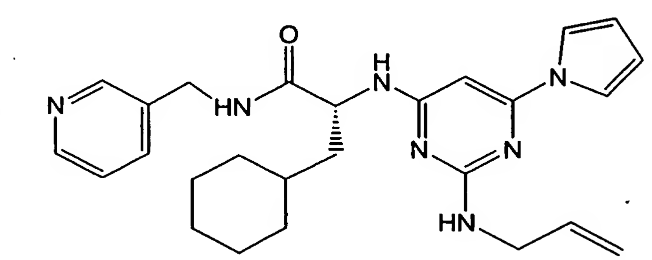
	774868
	1828493
	866399
	867894

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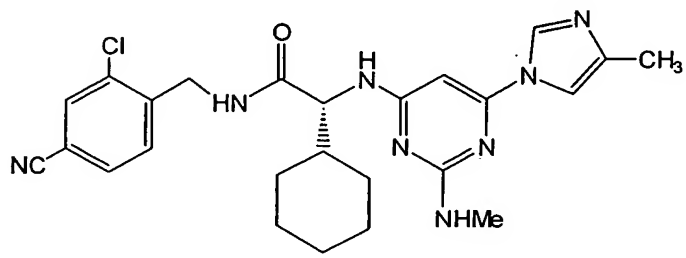
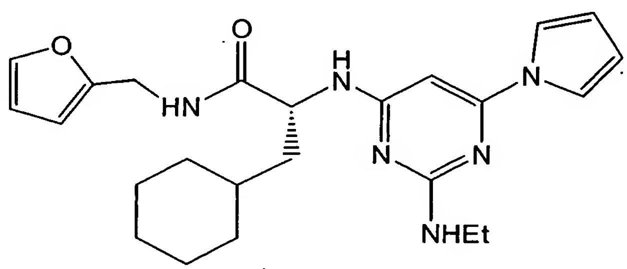
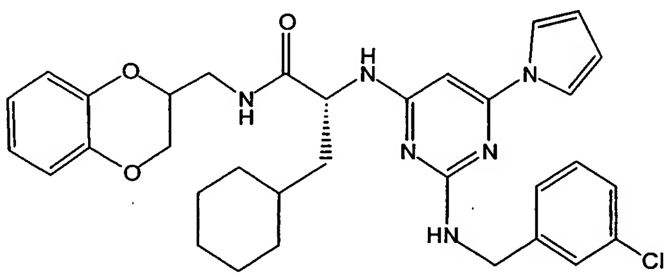
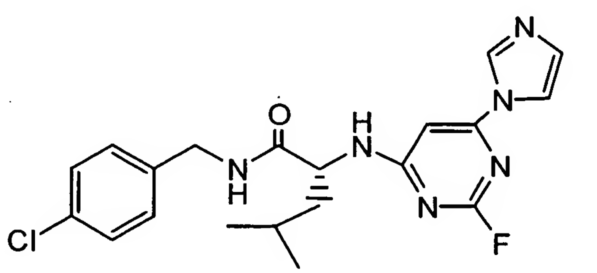
	870562
	917930
	928221
	953837

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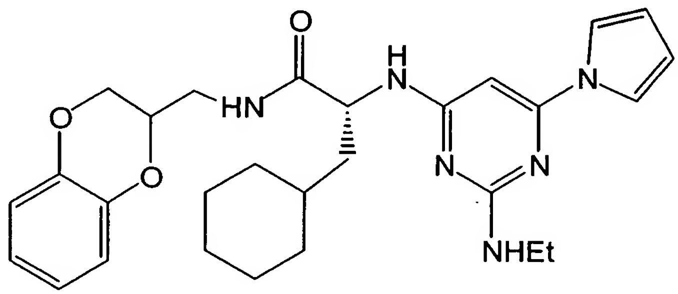	480759